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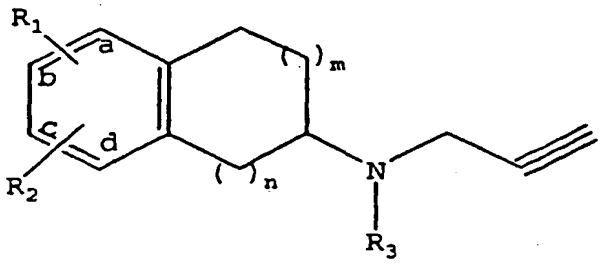
(54) Title: PROPARGYLAMINO INDAN DERIVATIVES AND PROPARGYLAMINO TETRALIN DERIVATIVES AS BRAIN-SELECTIVE MAO INHIBITORS



(57) Abstract: The subject invention provides derivatives of propargylamino indan (PAI) and propargylamino tetralin that selectively inhibit monoamine oxidase (MAO) in the brain, having the structure:, wherein R_1 is OC (O) R_9 and R_2 is H, wherein R_9 i s branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or R_1 is OC (O) R_4 and R_2 is OC (O) R_4, wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6, wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted; wherein R_3 is H or C_1 to C_6 alkyl; wherein n is 0 or 1; and wherein m is 1 or 2, or a pharmaceutically acceptable salt thereof. Additionally, the subject invention provides methods of treating neurological disorders using these compounds, uses of these compounds for the manufacture of medicaments for treating neurological disorders and processes for synthesis of these compounds.

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Applicants: Eran Blaugrund et al.
Serial No.: 10/712,958
Filed: November 13, 2003
Exhibit 1

PROPARGYLAMINO INDAN DERIVATIVES AND PROPARGYLAMINO TETRALIN DERIVATIVES AS BRAIN-SELECTIVE MAO INHIBITORS

This application claims the benefit of U.S. Serial No. 10/085,674, filed February 27, 2002, the contents of which are hereby incorporated by reference.

Throughout this application, various references are referenced by short citations within parenthesis. Full citations for these references may be found at the end of the specification, immediately preceding the claims. These references, in their entireties, are hereby incorporated by reference to more fully describe the state of the art to which this invention pertains.

Field of the Invention

The subject of this invention provides for derivatives of propargylaminoindans and propargylaminotetralins that are irreversible inhibitors of the enzyme monoamine oxidase A and/or B and also for prodrugs for the administration of these compounds. Such compounds may be useful in the treatment of Parkinson's disease, Alzheimer's disease, depression and other neurological disorders.

Background of the Invention

The enzyme monoamine oxidase (MAO) plays an essential role in the metabolic degradation of important amine neurotransmitters including dopamine, serotonin and noradrenaline. Thus, agents that inhibit MAO are of potential therapeutic benefit for a variety of neurological disease indications, including Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), etc. (Szelnyi, I.; Bentue-Ferrer et al.; Loscher et al.; White et al.; U.S. Patent No. 5,744,500). Other diseases and conditions which have

been associated with toxic levels of monoamine oxidase-B are memory disorders (The interaction of L-deprenyl and scopolamine on spatial learning/memory in rats), panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD)(Potential applications for monoamine oxidase B inhibitors), attention deficit disorder (Kleyweg), and Tourette's syndrome (Treatment of Tourette's: Overview).

Many inhibitors of MAO are chiral molecules (U.S. Patent No. 5,744,500). Although one enantiomer often shows some stereoselectivity in relative potency towards MAO-A and -B, a given enantiomeric configuration is not always more selective than its isomer in discriminating between MAO-A and -B (Hazelhoff et al., Naunyn-Schmeideberg's Arch. Pharmacol.).

MAO inhibitors can also be classified as reversible inhibitors which inhibit the enzyme by a competitive mechanism or as irreversible inhibitors which are generally mechanism based (suicide inhibitors) (Dostert). For example, moclobemide is a reversible MAO-A-specific inhibitor (Fitton et al.) developed as an anti-depressant. Likewise, rasagiline (U.S. Patent No. 5,744,500) and selegiline (Chrisp et al.) are MAO-B-selective irreversible inhibitors.

Irreversible inhibitors have the advantage of lower, less frequent dosing since their MAO inhibition is not based directly on the drugs' pharmacokinetic behavior, but rather on the *de novo* regeneration of the MAO enzyme.

MAO also plays an essential role in the oxidative deamination of biogenic and food-derived amines, both in the central nervous system and in peripheral tissues. MAO is found in two functional isoenzyme forms, MAO-A and MAO-B, each of which shows preferential affinity for substrates and specificity toward

inhibitors. Thus, MAO-A preferentially oxidizes serotonin, noradrenaline and adrenaline, whereas MAO-B preferentially metabolizes phenylethylamine. Dopamine is a substrate for both forms of the enzyme(Szelenyi, I.).

N-Propargyl-(1R)-aminoindan is known to be a potent B-selective inhibitor of MAO (U.S. Patent No. 5,457,133). Various derivatives of this compound have been prepared and shown to have varying degrees of potency and selectivity for the inhibition of MAO-A and/or -B. There is no currently accepted theory explaining the effect of structure on the activity (SAR) of the various substituted propargylaminoindans.

The dopamine agonistic activity and MAO inhibitory properties of 7-(methyl-prop-2-ynylamino)-tetralin-2-ol and 7-(methyl-prop-2-ynylamino)-tetralin-2,3-diol have been reported (Hazelhoff et al., Eur. J. Pharmacol.). The details of the synthesis of these compounds have not been published, however.

6,7-di-O-benzoyl-2-aminotetralin has been reported as a prodrug of the dopaminergic agonist 6,7-di-hydroxy-2-aminotetralin (Horn et al.). However, no N-propargyl derivatives were reported and the compounds were not shown to have MAO inhibitory or neuroprotective activities.

7-(propyl-prop-2-ynylamino)-tetralin-2-ol has been reported as an intermediate in the preparation of 7-[(3-iodoallyl)-propylamino]-tetralin-2-ol. Only the latter has been pharmacologically characterized as D_3-dopamine receptor ligand (Chumpradit et al.). No other N-alkyl substituents were described.

Florvall et al. report the preparation of amino acid-based prodrugs of amiflamine analogues. Amiflamine is a reversible MAO-A inhibitor.

PCT International Application No. PCT/US97/24155 concerns carbamate aminoindan derivatives, including propargylamines, as inhibitors of MAO-A and MAO-B for the treatment of Alzheimer's disease and other neurological conditions. However, the compounds of PCT/US97/24155 are not selective for MAO over acetylcholinesterase ("AChE"). Thus, the compounds generally inhibit acetylcholinesterase along with MAO. Acetylcholinesterase inhibition is a route implicated in certain neurological disorders, but is a different route from the route of MAO inhibition.

U.S. Patent No. 6,303,650 discloses derivatives of 1-aminoindan as selective MAO B inhibitors that additionally inhibit acetylcholinesterase. The reference teaches that its compounds can be used to treat depression, Attention Deficit Disorder (ADC), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other dementias such as senile dementia, dementia of the Parkinson's type, vascular dementia and Lewy body dementia.

Many irreversible MAO inhibitors contain the propargyl amine functionality. This pharmacophore is responsible for the MAO inhibitory activity of such compounds. Some propargylamines have been shown to have neuroprotective/neurorescue properties independent of their MAO inhibition activity (U.S. Patent No. 4,844,033; Krageten et al.).

PCT International Application No. PCT/IL96/00115 relates to pharmaceutical compositions comprising racemic, (S), and (R)-N-propargyl-1-aminoindan. (R)-N-propargyl-1-aminoindan selectively inhibits MAO-B in the treatment of Parkinson's disease and other neurological disorders (PCT/IL96/00115).

Derivatives of 1-aminoindan, including propargyl aminoindan, and their salts are described in many U.S. patents (U.S. Patents No.

5,639,913, 5,877,221, 5,880,159, 5,877,218, 5,914,349, 5,994,408) and a PCT International Application (PCT/US95/00245). These references disclose racemic, R and S enantiomers of 1-aminoindan derivatives for the treatment of Parkinson's disease and other neurological conditions (U.S. Patents No. 5,639,913, 5,877,221, 5,880,159, 5,877,218, 5,914,349, 5,994,408, PCT/US95/00245).

PCT International Application No. PCT/US97/24155 concerns aminoindan derivatives, including propargyl aminoindan, as inhibitors of MAO-A and MAO-B for the treatment of Parkinson's disease and other neurological conditions. The publication reveals that the disclosed compounds exhibit a greater selectivity for MAO-A and MAO-B in the brain than in the liver or intestine.

U.S. Patent No. 6,316,504 discloses that the R(+) enantiomer of N-propargyl-1-aminoindan is a selective irreversible inhibitor of MAO-B. The patent indicates that (R)-N-propargyl-1-aminoindan is useful for the treatment of Parkinson's disease, a memory disorder, dementia, depression, hyperactive syndrome, an affective illness, a neurodegenerative disease, a neurotoxic injury, stroke, brain ischemia, a head trauma injury, a spinal trauma injury, neurotrauma, schizophrenia, an attention deficit disorder, multiple sclerosis, and withdrawal symptoms.

European Patent No. 436492 discloses the R enantiomer of N-propargyl-1-aminoindan as a selective irreversible inhibitor of MAO-B in the treatment of Parkinson's disease and other neurological conditions. Numerous U.S. patents also relate to the MAO B inhibition of (R)-N-propargyl-1-aminoindan and its use for treating patients suffering from Parkinson's Disease and other neurological disorders (U.S. Patents No. 5,387,612, 5,453,446, 5,457,133, 5,519,061, 5,532,415, 5,576,353,

5,668,181, 5,744,500, 5,786,390 and 5,891,923).

PCT International Application No. PCT/IL97/00205 discloses S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof for the treatment of a neurological disorder of neurotrauma or for improving memory. The compounds were found to be neuroprotective, but not inhibitory of MAO-A or MAO-B (PCT/IL97/00205).

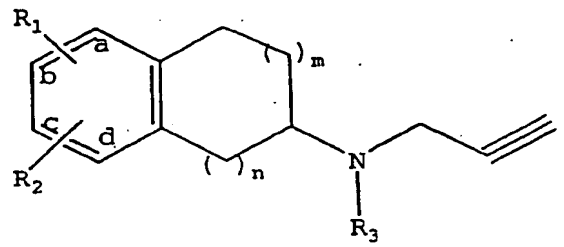
U.S. Patent No. 5,486,541 provides N-propargyl-1-amonoindan monofluorinated in the phenyl ring as selective inhibitors of MAO-B. These compounds are presented as useful in the treatment of Parkinson's disease, memory disorders, dementia of the Alzheimer's type, depression and the hyperactive syndrome in children.

Among the many derivatives of propargylaminoindan mentioned in the prior art are hydroxy-propargylaminoindans. U.S. Patent No. 3,513,244 lists some racemic N-propargylamino indanols and tetralinols for use as antihypertensives. These compounds are not exemplified chemically and are not pharmacologically characterized (U.S. Patent No. 3,513,244).

N-propargylamino indanol also appears in E.P. 267024 as a hydrofluorene derivative, i.e., 3-amino-4-indanol (7-OH fluorene). The hydrofluorene derivatives and salts in E.P. 267024 are employed as cerebral activators in the treatment of anoxemia and hypoxemia. In addition, such derivatives help prevent arrhythmia and heart failure caused by lack of oxygen (E.P. 267024). The derivatives also act as antioxidants and cholinergic nerve system activating agents (E.P. 267024).

Summary of the Invention

The subject invention provides a compound having the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

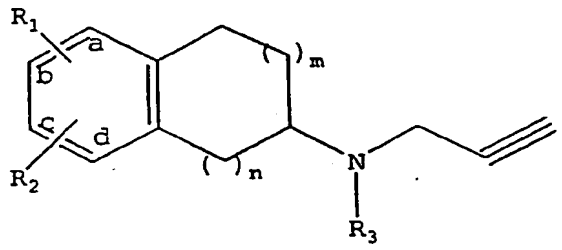
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof.

The subject invention also provides a compound having the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

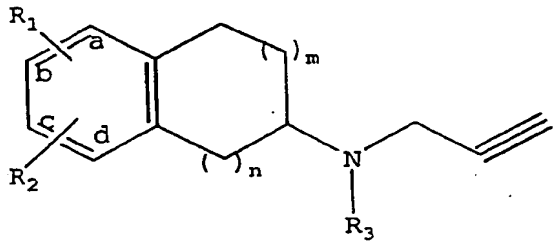
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein n is 0 or 1, and m is 1 or 2; and

wherein R_3 is H or Me when n is 1 and m is 1, or R_3 is H or C_1 to C_6 alkyl when n is 0 or m is 2,

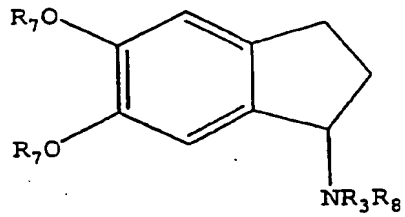
or a pharmaceutically acceptable salt thereof.

In addition, the subject invention provides a compound having the structure:



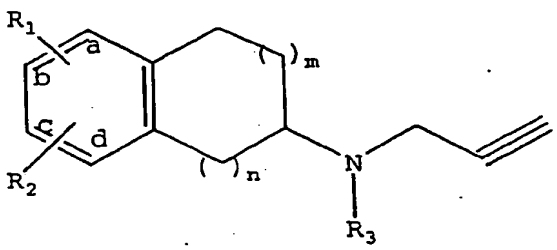
wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

The subject invention further provides a compound having the structure:



wherein R_7 is H, C_1 to C_6 alkyl, aryl, aralkyl or $C(O)R_4$,
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein R_8 is H or t-butoxycarbonyl (Boc).

The subject invention also provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

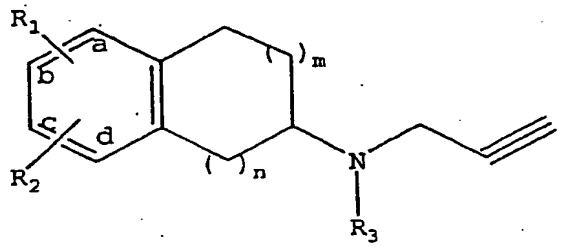
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

Furthermore, the subject invention provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;

wherein R_2 is H or $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

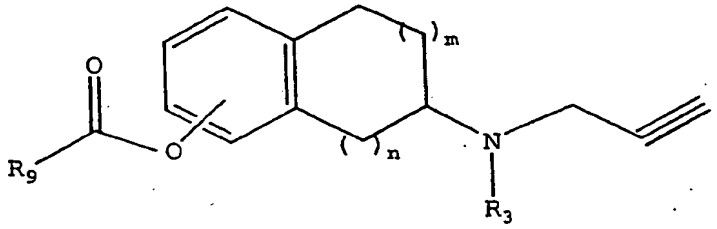
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

The subject invention additionally provides a process for preparing a compound having the structure:

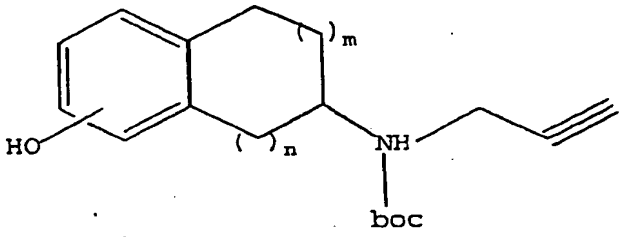


wherein n is 0 or 1, and m is 1 or 2;

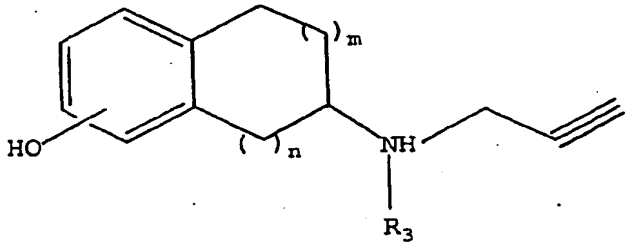
wherein R_3 is H or C_1 to C_6 alkyl; and

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

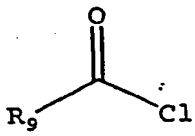
comprising the step of reacting



or

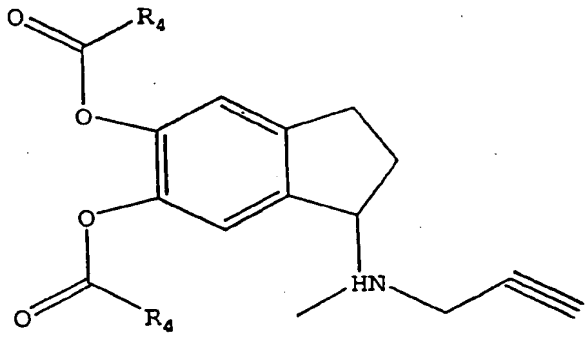


with



in the presence of an acid or 4-dimethylaminopyridine (DMAP) to form the compound.

The subject invention also provides a process for preparing a compound having the structure:

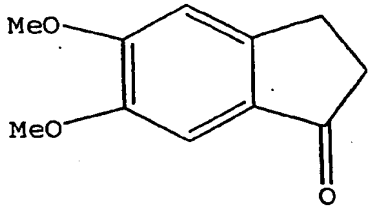


wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

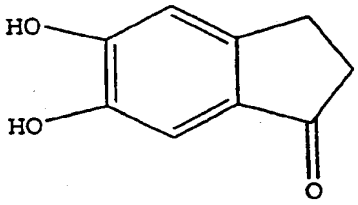
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

which process comprises:

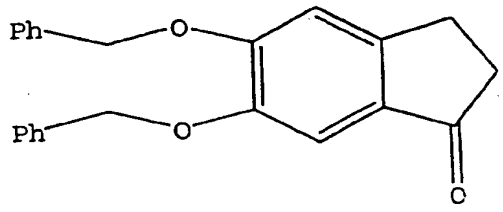
(a) reacting a compound having the structure:



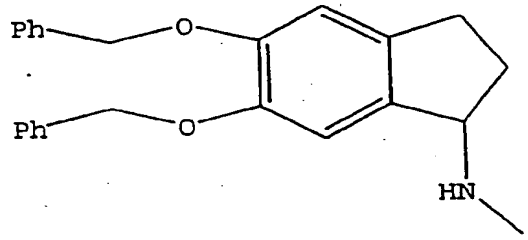
with $AlCl_3$ or BBr_3 in the presence of toluene to produce a compound having the structure:



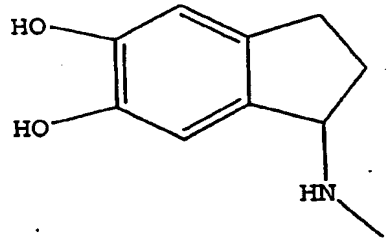
(b) reacting the product formed in step (a) with benzyl chloride and K_2CO_3 in the presence of dimethyl formamide (DMF) to produce a compound having the structure: .



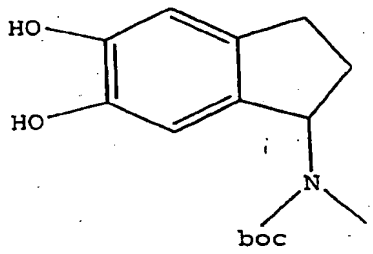
(c) reacting the product formed in step (b) with $MeNH_2 \cdot HCl$, $NaCNBH_3$ in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:



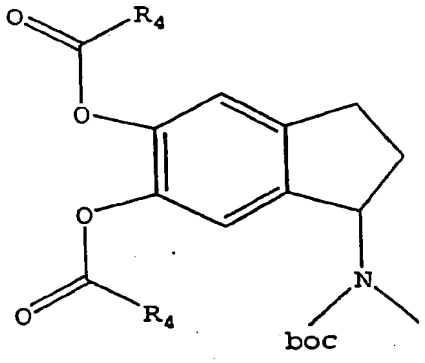
(d) reacting the product formed in step (c) with H_2, Pd/C and MeOH to produce a compound having the structure:



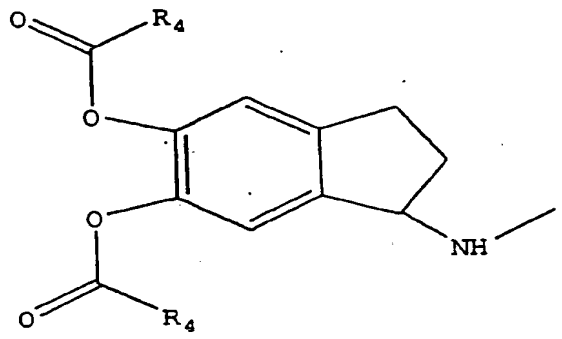
(e) reacting the product formed in step (d) with Boc_2O, dioxane/H_2O and $NaHCO_3$ to produce a compound having the structure:



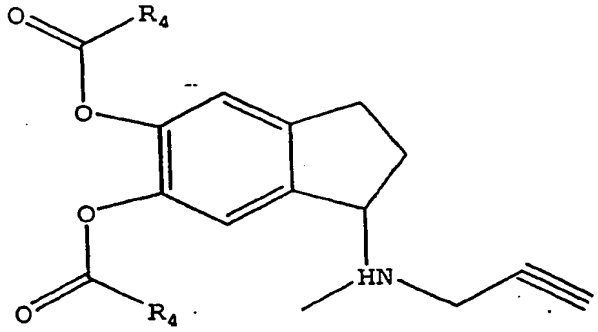
(f) reacting the product formed in step (e) with R_4COCl, Et_3N in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:



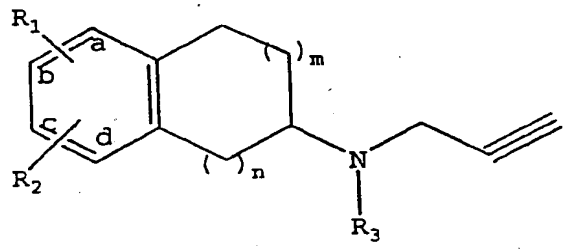
(g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:



(h) reacting the product formed in step (g) with propargyl bromide, K_2CO_3 in CH_3CN and then with HCl/ether and MeOH to produce a compound having the structure:



The subject invention also provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;

wherein R_2 is H, OH or $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

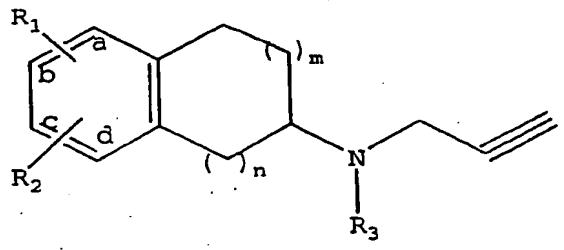
wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for treating a subject afflicted with a neurological disease, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

Additionally, the subject invention provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_4 is C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

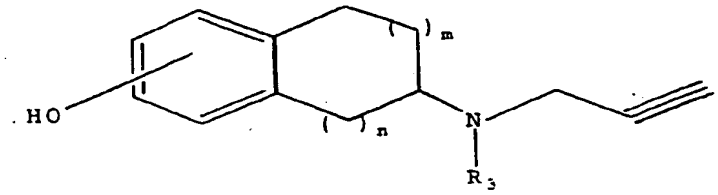
wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neurological disease in a subject, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

Description of the Drawings

Figure 1 presents routes for the manufacture of compounds with the following structures:



and

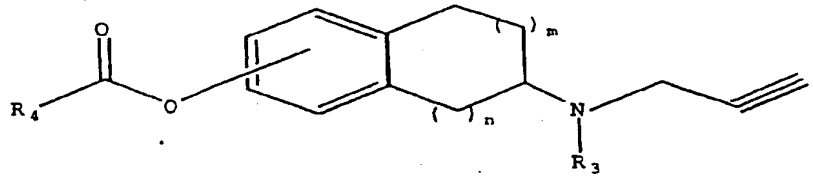
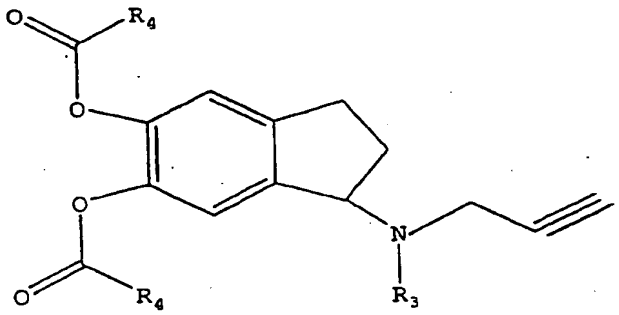
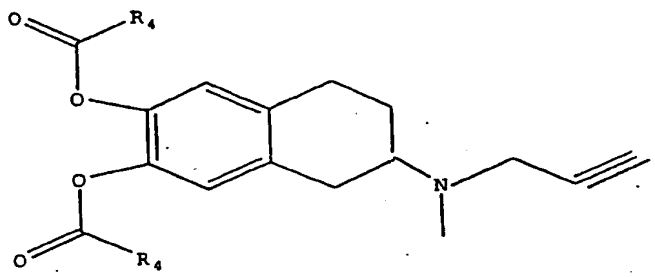


Figure 2 displays routes for the manufacture of a compound with the following structure:

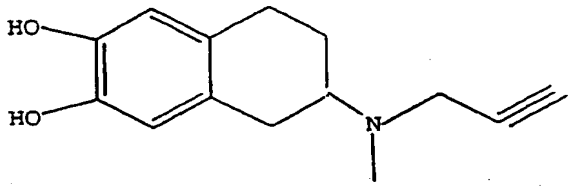


In Figure 2, the letters a) - i) are used to designate the following: a) $AlCl_3$, toluene; b) BnCl, K_2CO_3, DMF; c) R_3-NH_2, HCl, $NaCNBH_3$, THF/MeOH; d) H_2, Pd/C, MeOH; e) Boc_2O, dioxane/H_2O, $NaHCO_3$; f) R_4-COCl, Et_3N, DMAP, CH_2Cl_2; g) HCl/dioxane; h) propargyl bromide, K_2CO_3, CH_3CN; and i) HCl/ether, MeOH.

Figure 3 depicts routes for the manufacture of compounds with the structures:



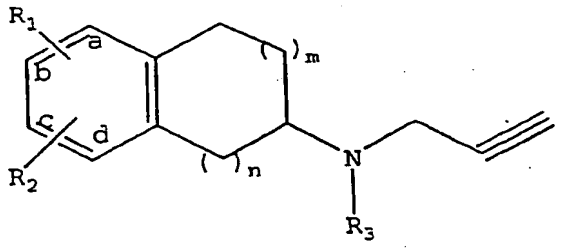
and



In Figure 3, the letters g) - l) are used to designate the following: g) $NaCNBH_3$, NH_4OAc; h) propargyl bromide, ACN, K_2CO_3; i) $NaCNBH_3$, paraformaldehyde; j) N-methylpropargylamine, $NaCNBH_3$; k) BBr_3; and l) R_4COCl, TFA or DMAP.

Detailed Description of the Invention

The subject invention provides a compound having the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

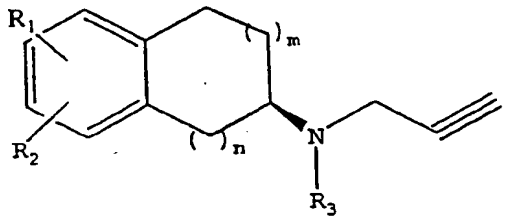
wherein n is 0 or 1; and

wherein m is 1 or 2,

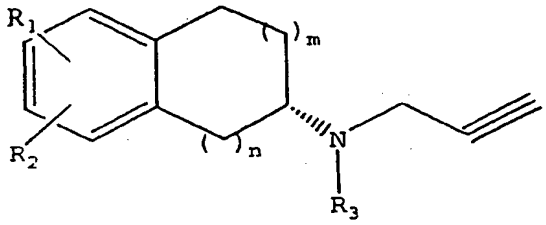
or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

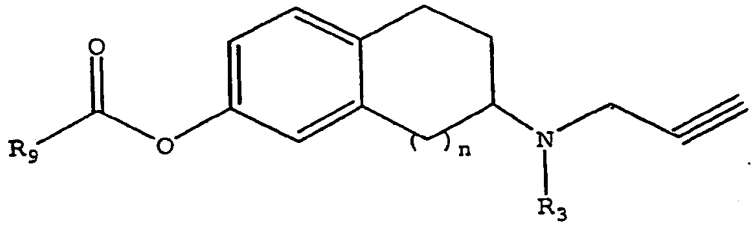
In another embodiment, the compound has the structure:



In a further embodiment, the compound has the structure:

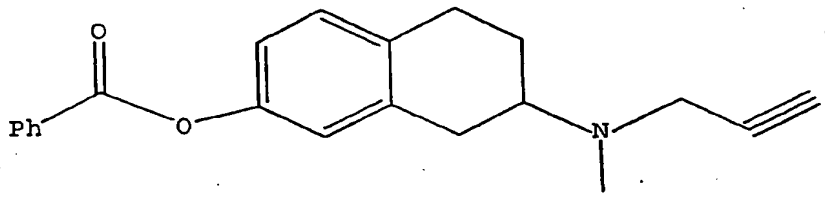


In yet another embodiment, the compound has the structure:



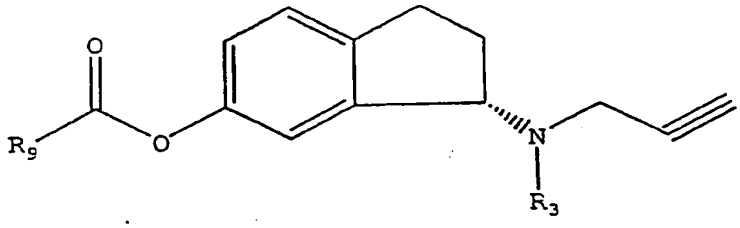
In one embodiment, n is 1.

In a further embodiment, the compound has the structure:

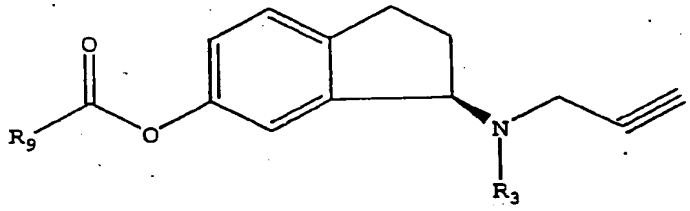


In an added embodiment, n is 0.

In yet another embodiment, the compound has the structure:



In still another embodiment, the compound has the structure:



In one embodiment, R_9 is Me and R_3 is H.

In another embodiment, R_9 is tBu and R_3 is H.

In a further embodiment, R_9 is nBu and R_3 is H.

In yet another embodiment, R_9 is CH_2Ph and R_3 is H.

In an additional embodiment, R_9 is Ph and R_3 is H.

In still another embodiment, wherein R_9 is Me and R_3 is Me.

In a further embodiment, R_9 is nBu and R_3 is Me.

In one embodiment, R_9 is Ph and R_3 is Me.

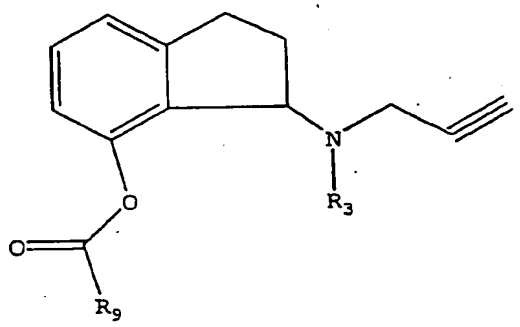
In an added embodiment, R_9 is tBu and R_3 is Me.

In another embodiment, R_9 is Ph(Me) and R_3 is Me.

In still another embodiment, R_9 is $Ph(OMe)_2$ and R_3 is Me.

In a further embodiment, R_9 is $Ph(OMe)_2$ and R_3 is H.

In one embodiment, the compound has the structure:

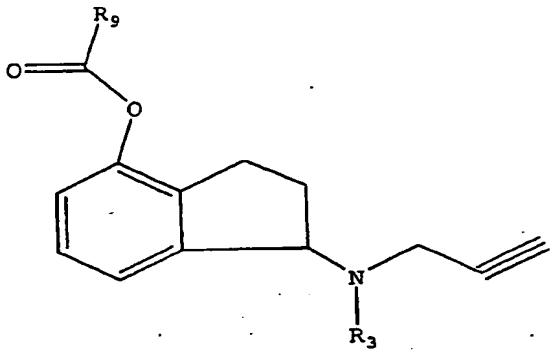


In an additional embodiment, R_3 is Me and R_9 is Me.

In a further embodiment, R_3 is Me and R_9 is Ph.

In another embodiment, R_3 is Me and R_9 is $Ph(OMe)_2$.

In yet another embodiment, the compound has the structure:

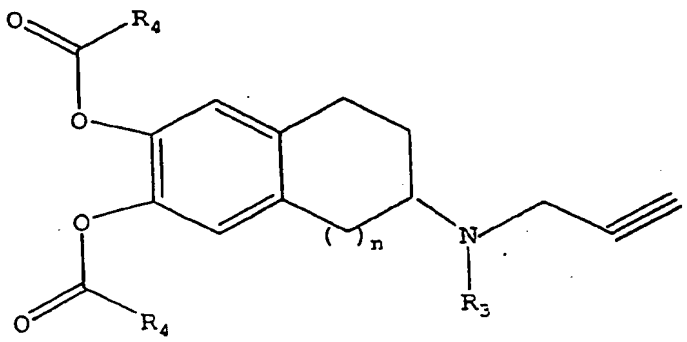


In an added embodiment, R_3 is Me and R_9 is Me.

In still another embodiment, R_3 is H and R_9 is Ph.

In one embodiment, R_3 is H and R_9 is $Ph(OMe)_2$.

In another embodiment, the compound has the structure:



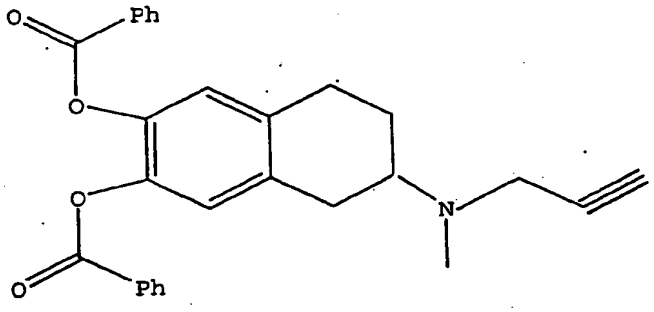
In a further embodiment, n is 0.

In yet another embodiment, R_4 is Ph and R_3 is Me.

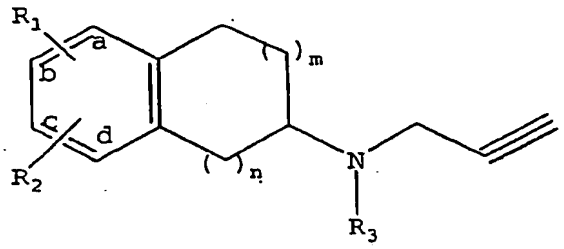
In one embodiment, n is 1.

In still another embodiment, R_3 is Me.

In an added embodiment, the compound has the structure:



The subject invention also provides a compound having the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

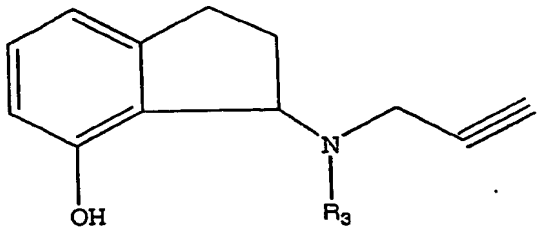
wherein n is 0 or 1, and m is 1 or 2; and

wherein R_3 is H or Me when n is 1 and m is 1, or R_3 is H or C_1 to C_6 alkyl when n is 0 or m is 2,

or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

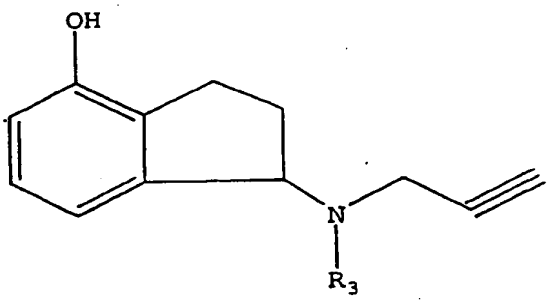
In another embodiment, the compound has the structure:



In an additional embodiment, R_3 is H.

In a further embodiment, R_3 is Me.

In yet another embodiment, the compound has the structure:

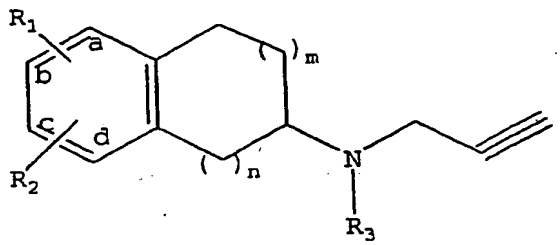


In still another embodiment, R_3 is H.

In one embodiment, R_3 is Me.

In a further embodiment, n is 0.

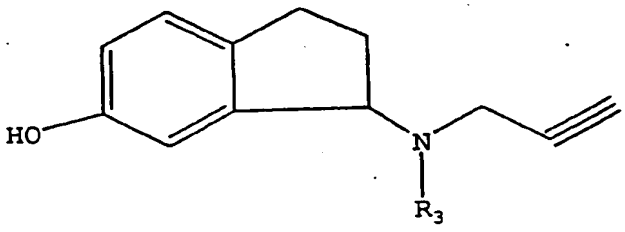
Additionally, the subject invention provides a compound having the structure:



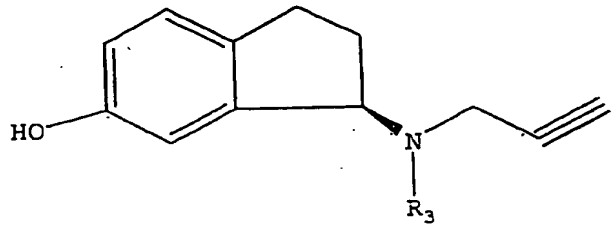
wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

In a further embodiment, the compound has the structure:



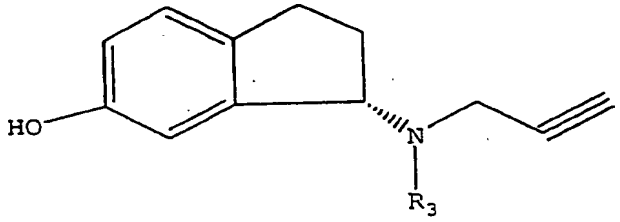
In another embodiment, the compound has the structure:



In an added embodiment, R_3 is H.

In yet another embodiment, R_3 is Me.

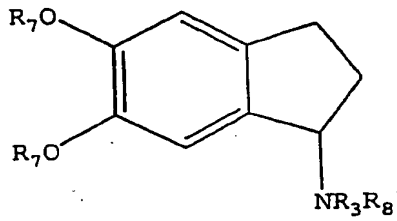
In a further embodiment, the compound has the structure:



In one embodiment, R_3 is H.

In another embodiment, R_3 is Me.

The subject invention further provides a compound having the structure:



wherein R_7 is H, C_1 to C_6 alkyl, aryl, aralkyl or $C(O)R_4$,

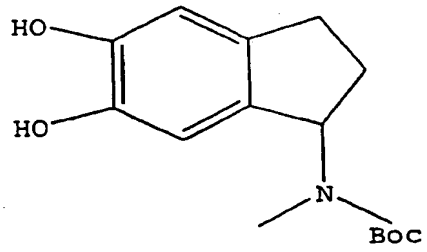
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

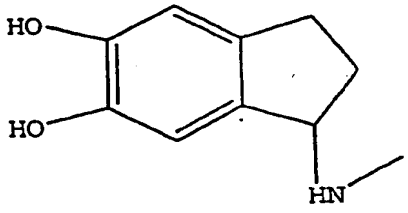
wherein R_3 is H or C_1 to C_6 alkyl;

wherein R_8 is H or t-butoxycarbonyl (Boc).

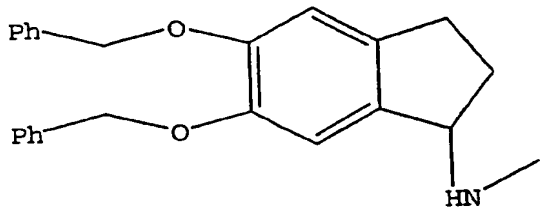
In one embodiment, the compound has the structure:



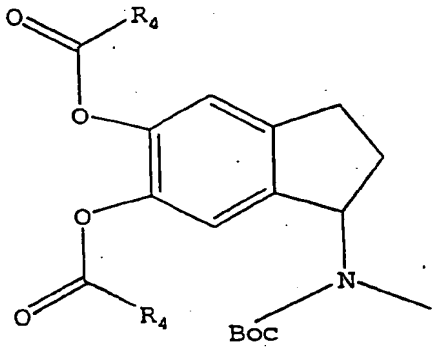
In another embodiment, the compound has the structure:



In still another embodiment, the compound has the structure:

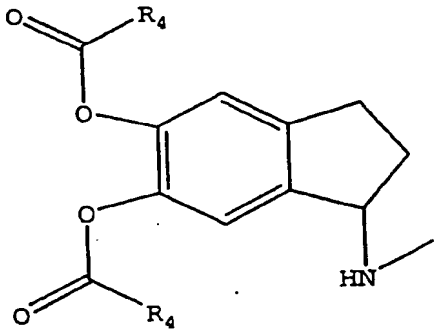


In an added embodiment, the compound has the structure:



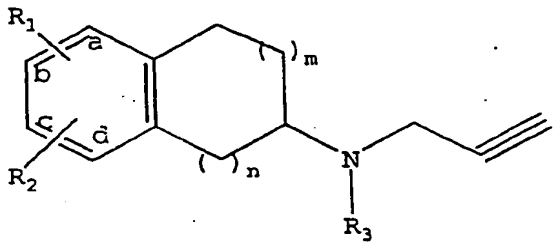
In yet another embodiment, R_4 is Ph.

In one embodiment, the compound has the structure:



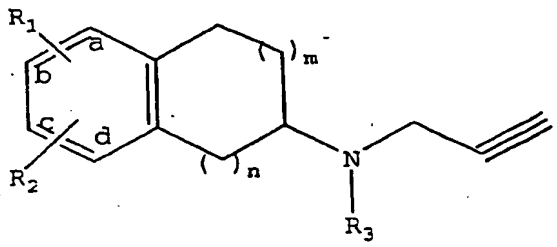
In a further embodiment, R_4 is Ph.

The subject invention additionally provides a pharmaceutical composition comprising a compound having the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or
R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

The subject invention further provides a pharmaceutical composition comprising a compound having the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

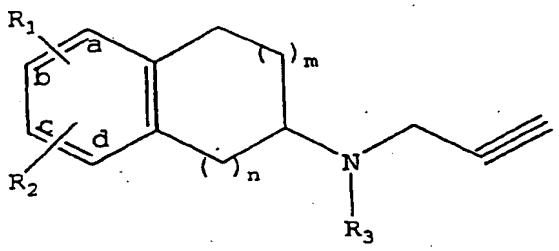
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein n is 0 or 1, and m is 1 or 2; and

wherein R_3 is H or Me when n is 1 and m is 1, or R_3 is H or C_1 to C_6 alkyl when n is 0 or m is 2,

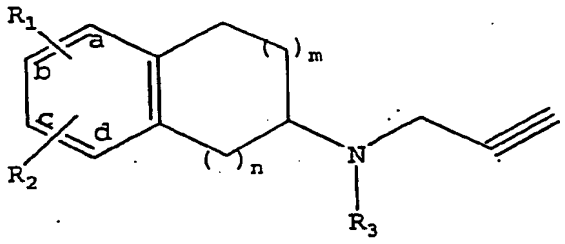
or a pharmaceutically acceptable salt thereof.

The subject invention also provides a pharmaceutical composition comprising a compound having the structure:



wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

The subject invention also provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;

wherein R_2 is H, OH or $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

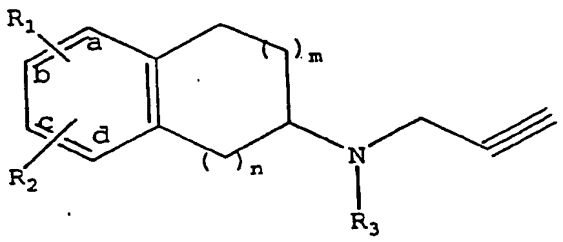
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

Additionally, the subject invention provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

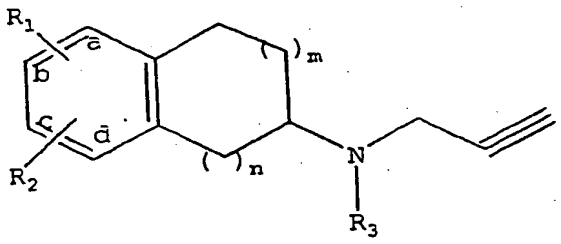
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

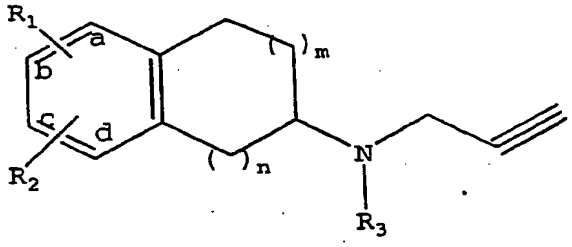
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

In one embodiment of the method, the compound has the structure:



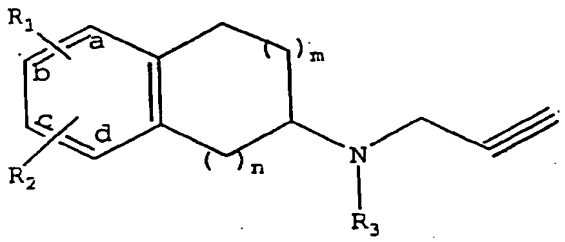
wherein R_1 is $OC(O)R_9$ and R_2 is H,
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or
R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

In another embodiment of the method, the compound has the structure:



wherein R_1 is OH;
wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or
R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;
wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

In a further embodiment of the method, the compound has the structure:



wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

In one embodiment, the subject is human.

In a further embodiment, the administration comprises oral, parenteral, intravenous, transdermal, or rectal administration.

In one embodiment, the effective amount is from about 0.01 mg per day to about 100.0 mg per day.

In yet another embodiment, the effective amount is from about 0.01 mg per day to about 50.0 mg per day.

In still another embodiment, the effective amount is from about 0.1 mg per day to about 100.0 mg per day.

In an added embodiment, the effective amount is from about 0.1 mg per day to about 10.0 mg per day.

In yet another embodiment, the effective amount is from about 0.01 mg to about 100.0 mg.

In one embodiment, the effective amount is from about 0.01 mg to about 50.0 mg.

In a further embodiment, the effective amount is from about 0.1 mg to about 100.0 mg.

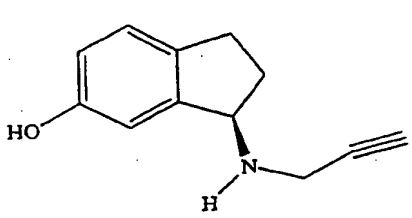
In another embodiment, the effective amount is from about 0.1 mg to about 10.0 mg.

In an additional embodiment, the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome. The

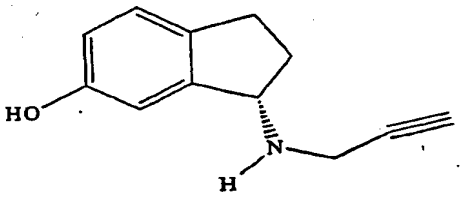
disease may also be neuropathy, hyperactive syndrome, neurotrauma, stroke, Parkinson's disease, Huntington's disease, and other dementia such as senile dementia, dementia of the vascular dementia or Lewy body dementia.

In still another embodiment, the neurological disease is depression.

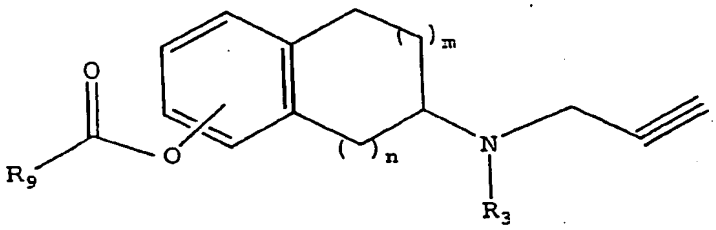
In still another embodiment, the compound has the structure:



or

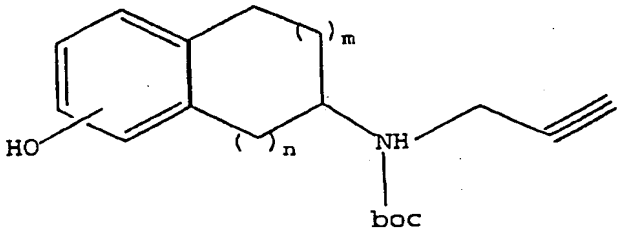


The subject invention further provides a process for preparing a compound having the structure:

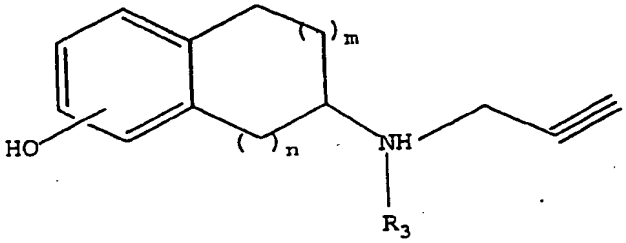


wherein n is 0 or 1, and m is 1 or 2;
wherein R_3 is H or C_1 to C_6 alkyl; and
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

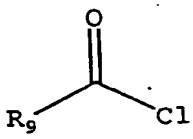
comprising the step of reacting



or

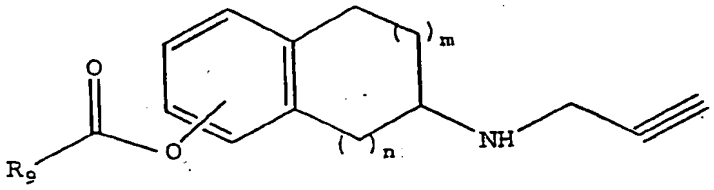


with



in the presence of an acid or 4-dimethylaminopyridine (DMAP) to form the compound.

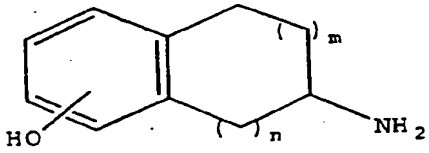
The subject invention also provides a process for preparing a compound having the structure:



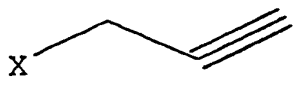
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

which process comprises:

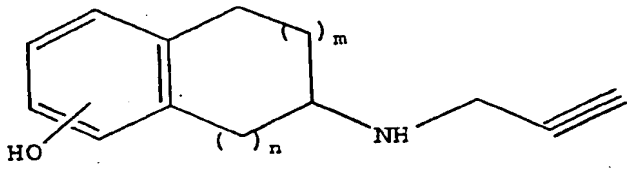
(a) reacting a compound having the structure:



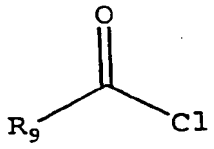
with a compound having the structure:



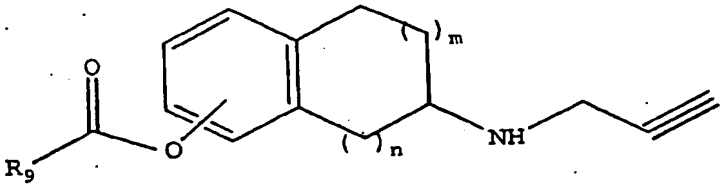
wherein X is a leaving group,
to produce a compound having the structure:



(b) reacting the compound formed in step (a) with a compound having the structure:

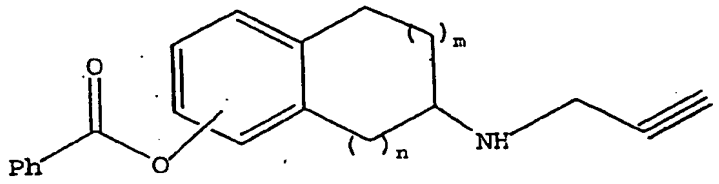


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to produce a compound having the structure:



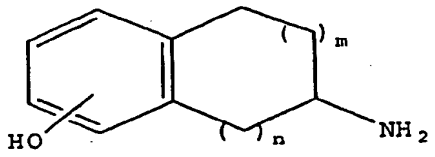
In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (b) is $CHCl_3$.

The subject invention further provides a process for preparing a compound having the structure:

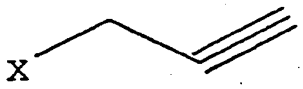


which comprises:

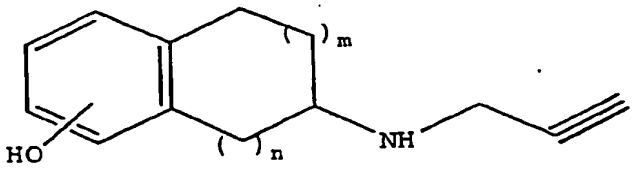
(a) reacting a compound having the structure:



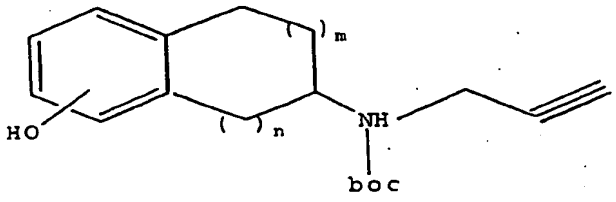
with a compound having the structure:



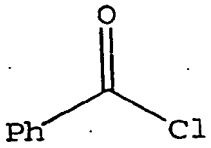
wherein X is a leaving group,
to produce a compound having the structure:



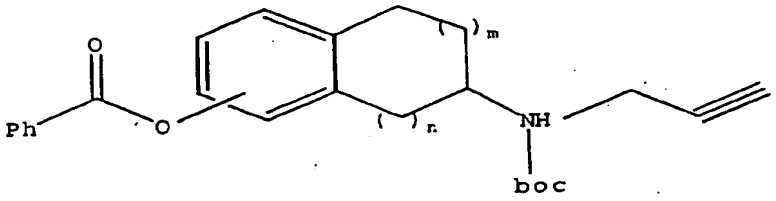
(b) N-protecting the compound formed in step (a) with tert-butoxycarbonyl (Boc) to produce a compound having the structure:



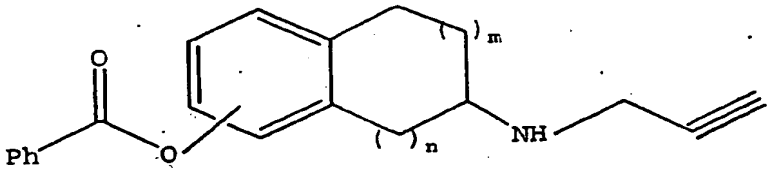
(c) reacting the compound formed in step (b) with a compound having the structure:



in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

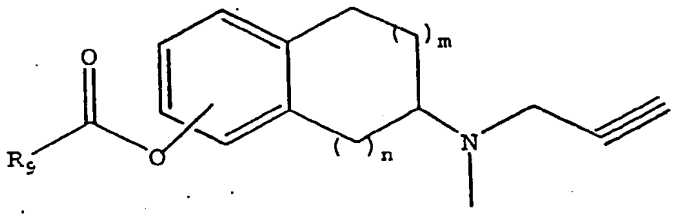


(d) deprotecting the compound formed in step (c) with HCl to produce a compound having the structure:



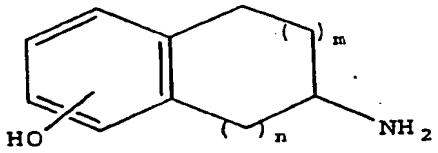
In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (b) is $CHCl_3$.

The subject invention additionally provides a process for preparing a compound having the structure:

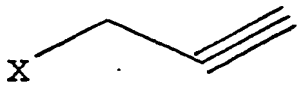


wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
which process comprises:

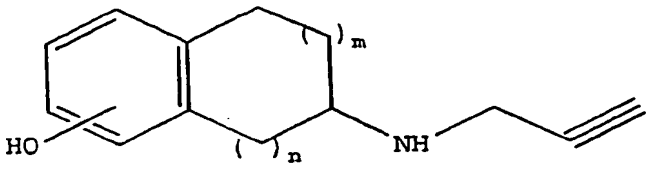
(a) reacting a compound having the structure:



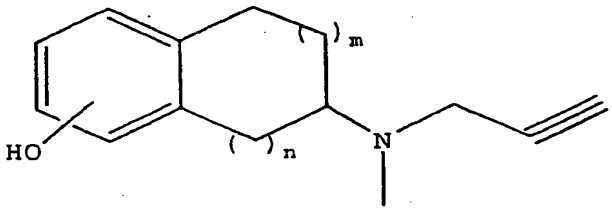
with a compound having the structure:



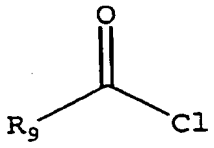
wherein X is a leaving group,
to produce a compound having the structure:



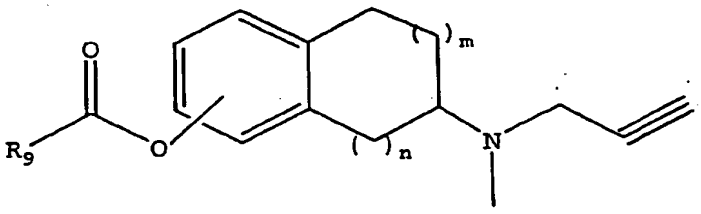
(b) reacting the compound formed in step (a) with $NaCNBH_3$ and paraformaldehyde to produce a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

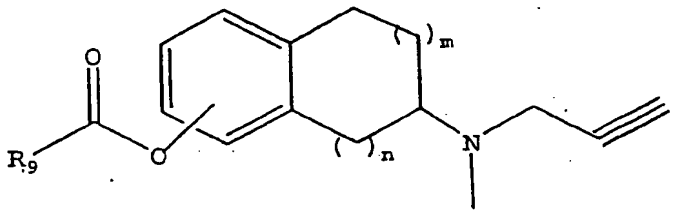


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



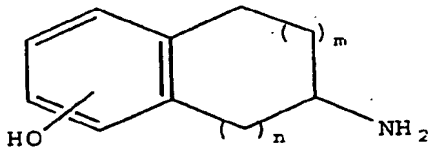
In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is $CHCl_3$.

The subject invention provides another process for preparing a compound having the structure:

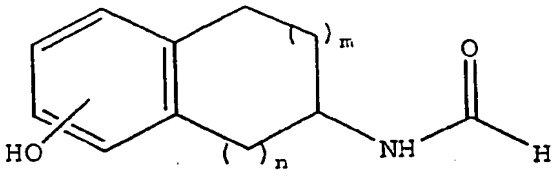


wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
which process comprises:

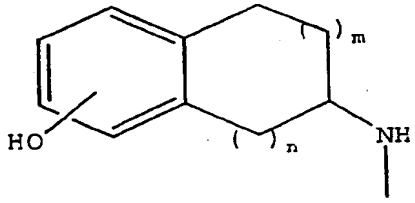
(a) reacting a compound having the structure:



with ethyl formate to produce a compound having the structure:

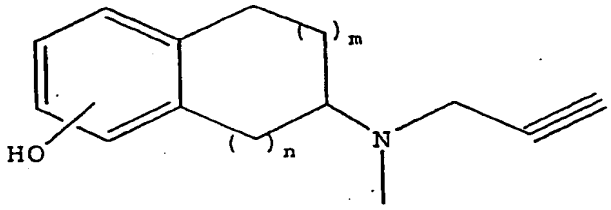


(b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:

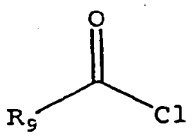


(c) reacting the compound formed in step (b) with a compound having the structure:

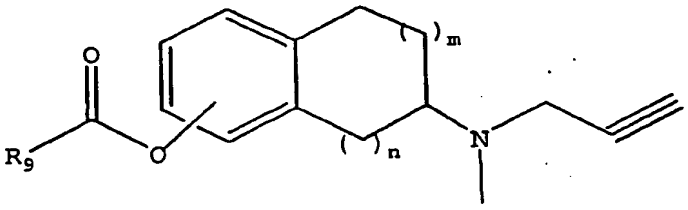
wherein X is a leaving group,
to form a compound having the structure:



(d) reacting the compound formed in step (c) with a compound having the structure:

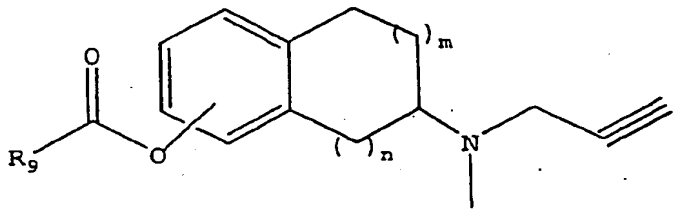


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



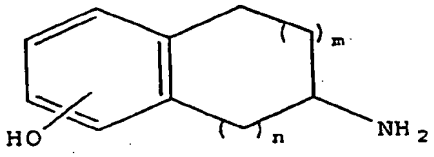
In one embodiment, the aprotic solvent in step (c) is $CHCl_3$.

The subject invention provides yet another process for preparing a compound having the structure:

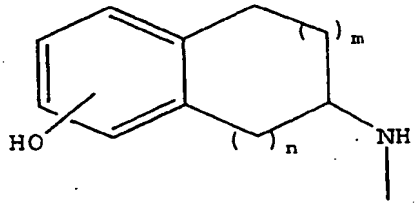


wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
which process comprises:

(a) reacting a compound having the structure:



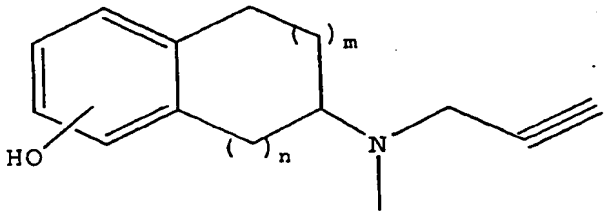
with $NaCNBH_3$/paraformaldehyde to produce a compound having the structure:



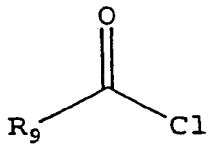
(b) reacting the compound formed in step (a) with a compound having the structure:

wherein X is a leaving group,

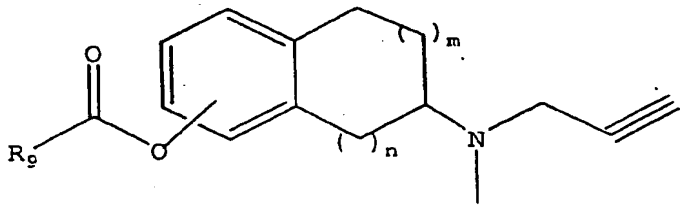
to form a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

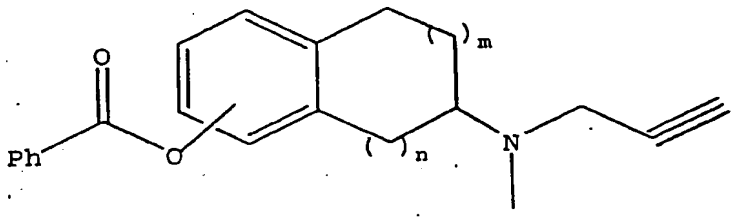


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



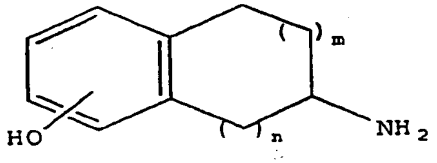
In one embodiment, the aprotic solvent in step (d) is $CHCl_3$.

Additionally, the subject invention provides a process for preparing a compound having the structure:



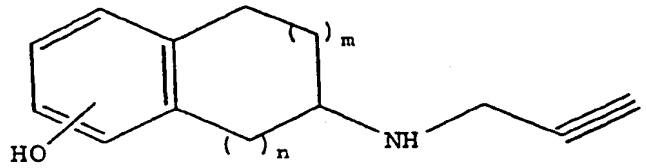
which comprises:

(a) reacting a compound having the structure:

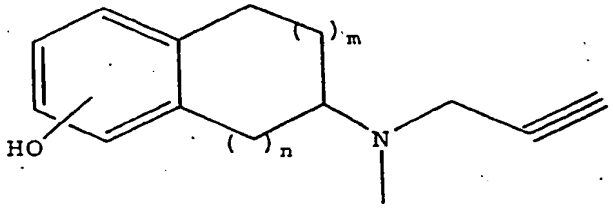


with a compound having the structure:

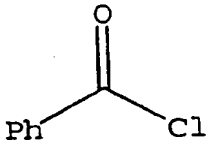
wherein X is a leaving group,
to produce a compound having the structure:



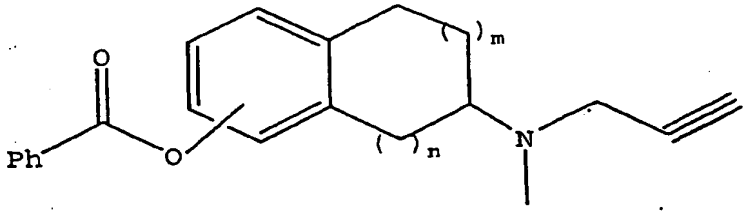
(b) reacting the compound formed in step (a) with $NaCNBH_3$ and paraformaldehyde to produce a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

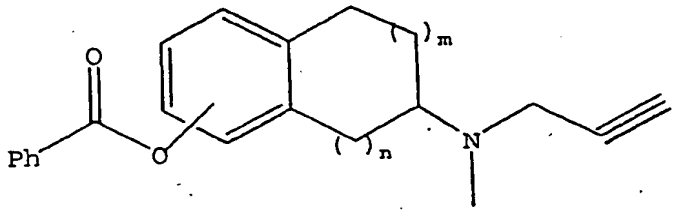


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



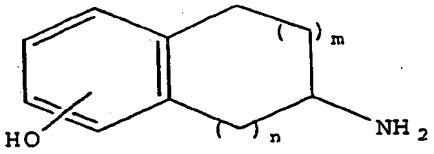
In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is $CHCl_3$.

The subject invention provides another process for preparing a compound having the structure:

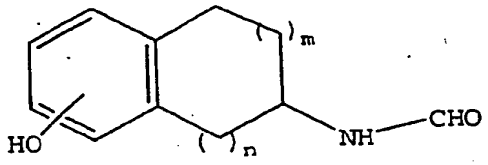


which comprises:

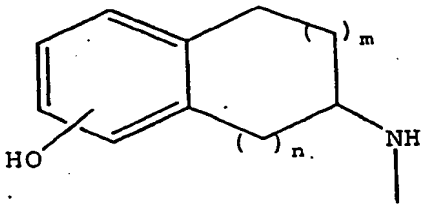
(a) reacting a compound having the structure:



with ethyl formate to produce a compound having the structure:

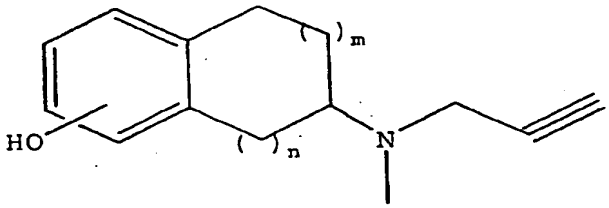


(b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:

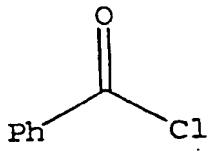


(c) reacting the compound formed in step (b) with a compound having the structure:

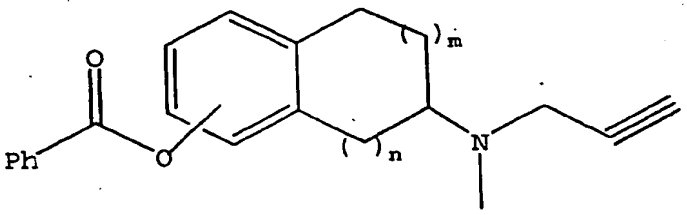
wherein X is a leaving group,
to form a compound having the structure:



(d) reacting the compound formed in step (c) with a compound having the structure:

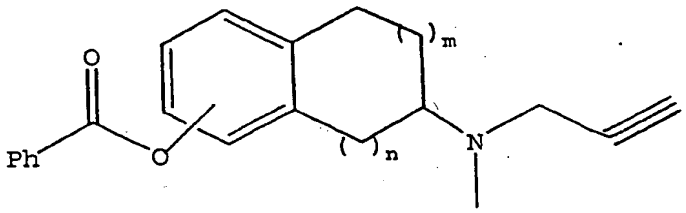


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



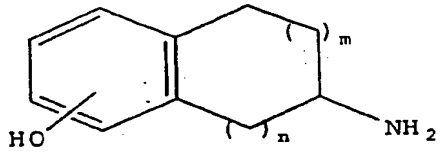
In one embodiment, the aprotic solvent in step (c) is $CHCl_3$.

The subject invention provides yet another process for preparing a compound having the structure:

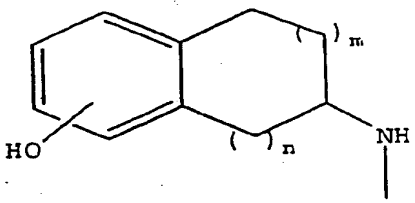


which comprises:

(a) reacting a compound having the structure:

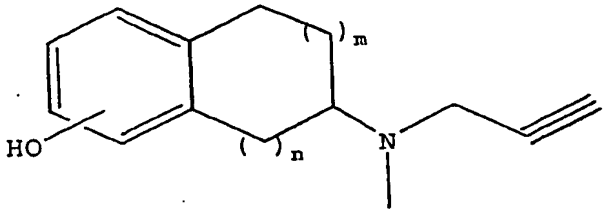


with $NaCNBH_3$/paraformaldehyde to produce a compound having the structure:

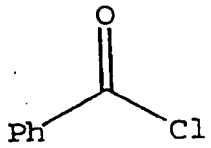


(b) reacting the compound formed in step (a) with a compound having the structure:

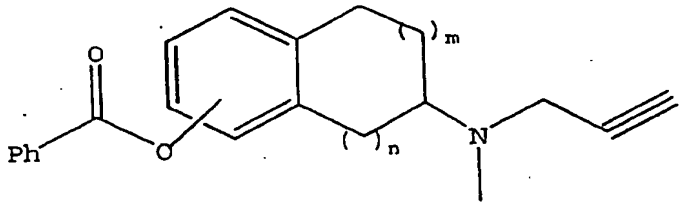
wherein X is a leaving group,
to form a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

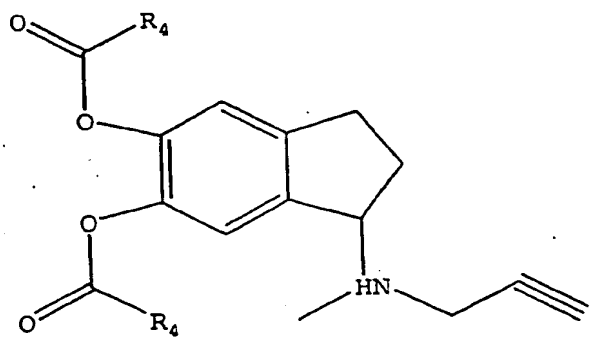


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



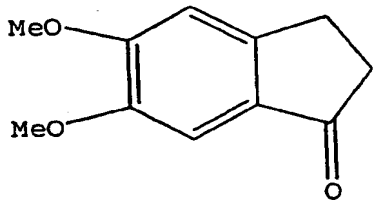
In one embodiment, the aprotic solvent in step (d) is $CHCl_3$.

The subject invention further provides a process for preparing a compound having the structure:

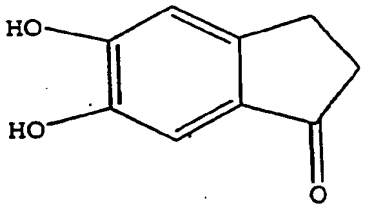


which comprises:

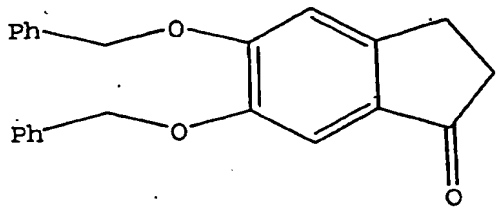
(a) reacting a compound having the structure:



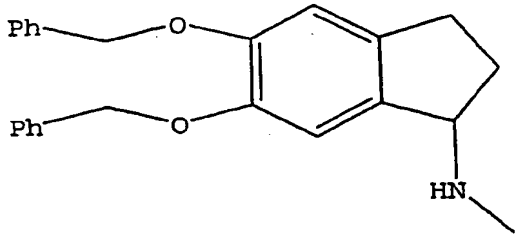
with $AlCl_3$ or BBr_3 in the presence of toluene to produce a compound having the structure:



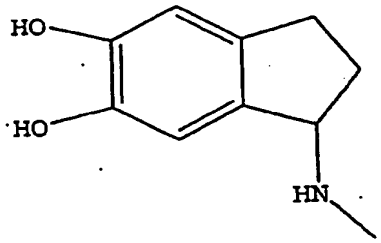
(b) reacting the product formed in step (a) with benzyl chloride and K_2CO_3 in the presence of dimethyl formamide (DMF) to produce a compound having the structure: .



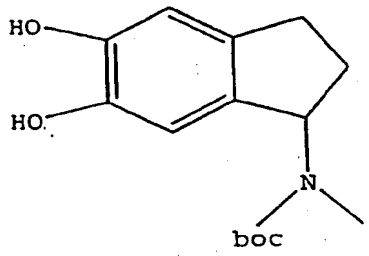
(c) reacting the product formed in step (b) with $MeNH_2 \cdot HCl$, $NaCNBH_3$ in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:



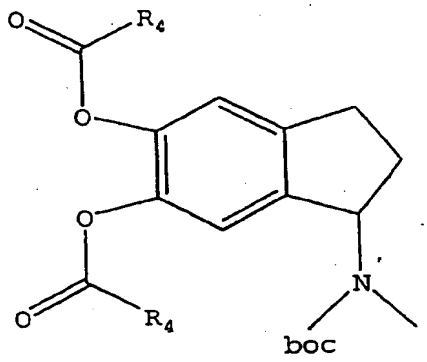
(d) reacting the product formed in step (c) with H_2, Pd/C and MeOH to produce a compound having the structure:



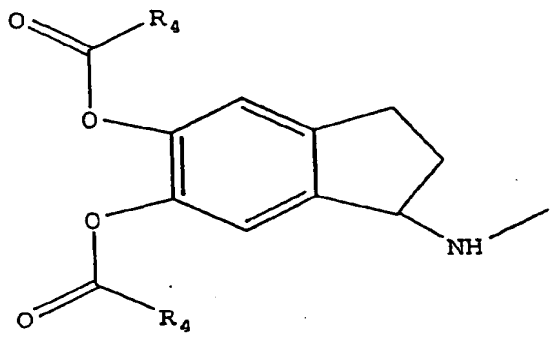
(e) reacting the product formed in step (d) with Boc_2O, dioxane/H_2O and $NaHCO_3$ to produce a compound having the structure:



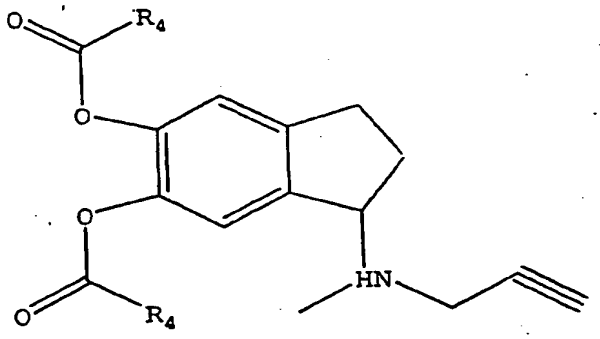
(f) reacting the product formed in step (e) with R_4COCl, Et_3N in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:



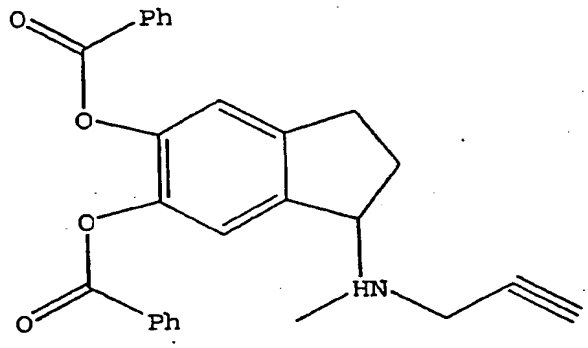
(g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:



(h) reacting the product formed in step (g) with propargyl bromide, K_2CO_3 in CH_3CN and then with HCl/ether and MeOH to produce a compound having the structure:

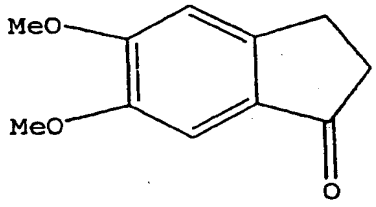


Also, the subject invention provides a process for preparing a compound having the structure:

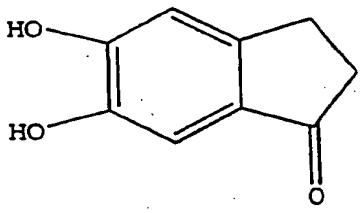


which comprises:

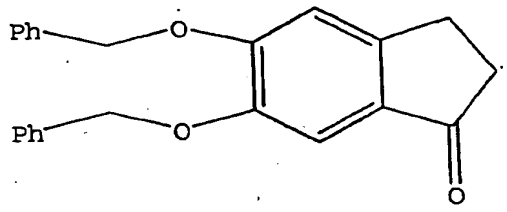
(a) reacting a compound having the structure:



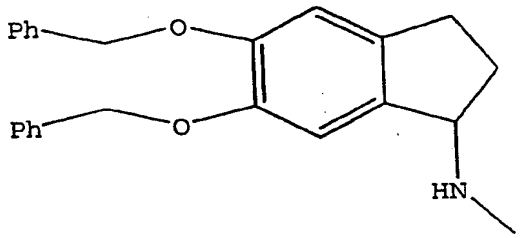
with $AlCl_3$ or BBr_3 in the presence of toluene to produce a compound having the structure:



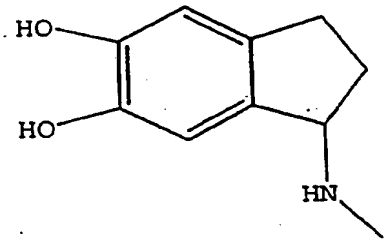
(b) reacting the product formed in step (a) with benzyl chloride and K_2CO_3 in the presence of dimethyl formamide (DMF) to produce a compound having the structure:



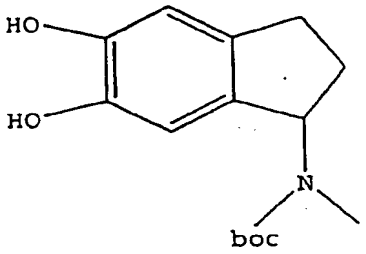
(c) reacting the product formed in step (b) with $MeNH_2 \cdot HCl$, $NaCNBH_3$ in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:



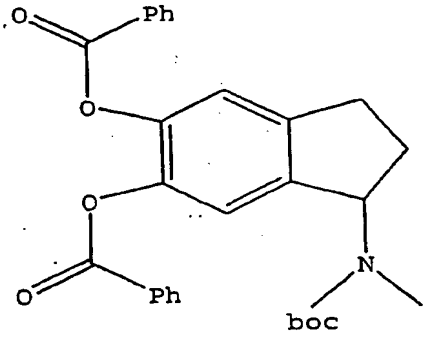
(d) reacting the product formed in step (c) with H_2, Pd/C and MeOH to produce a compound having the structure:



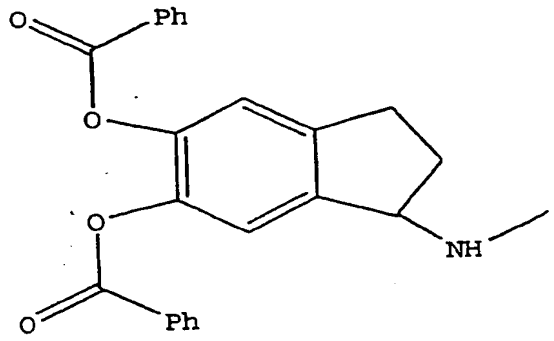
(e) reacting the product formed in step (d) with Boc_2O, dioxane/H_2O and $NaHCO_3$ to produce a compound having the structure:



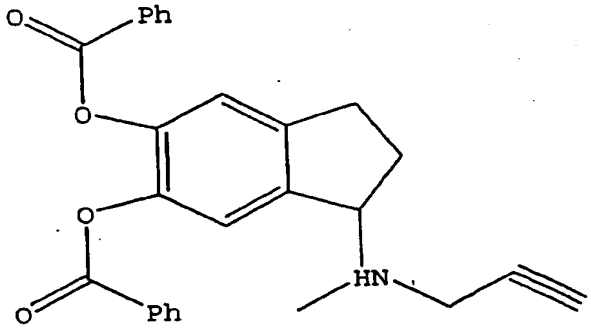
(f) reacting the product formed in step (e) with PhCOCl, Et_3N in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:



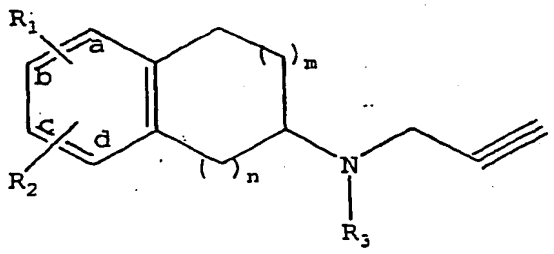
(g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:



(h) reacting the product formed in step (g) with propargyl bromide, K_2CO_3 in CH_3CN and then with HCl/ether and MeOH to produce a compound having the structure:



The subject invention further provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;

wherein R_2 is H, OH or $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

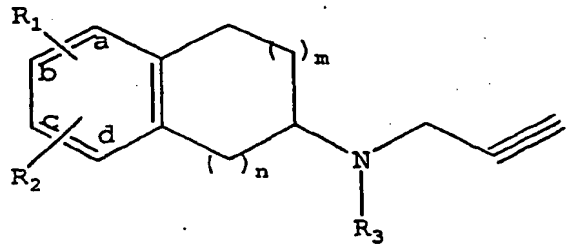
wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for treating a subject afflicted with a neurological disease, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

The subject invention also provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

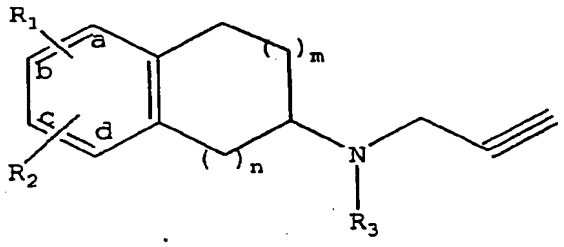
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neurological disease in a subject, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

In one embodiment of the use, the compound has the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

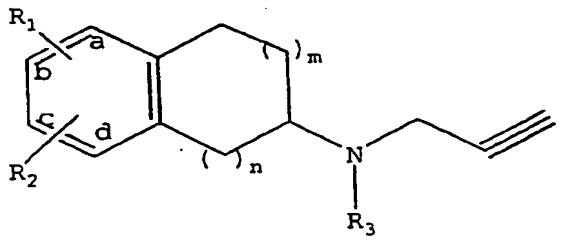
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

In another embodiment of the use, the compound has the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_3 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

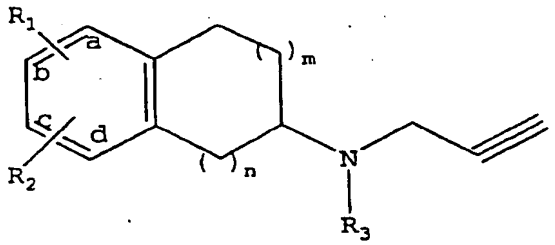
wherein R_5 and R_6 are each independently H, C_1 to C_6 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

In an additional embodiment of the use, the compound has the structure:



wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

In a further embodiment of the use, the subject is human.

In yet another embodiment of the use, the medicament is formulated for oral, parenteral, intravenous, transdermal, or rectal administration.

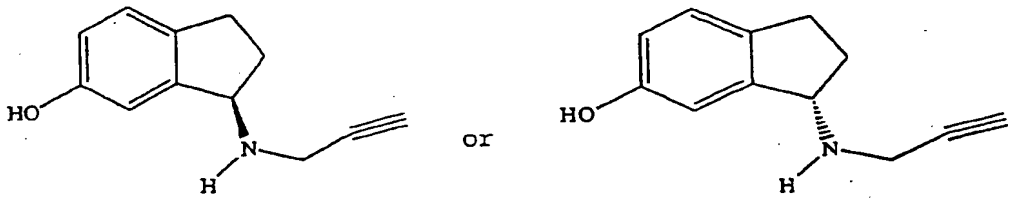
In an embodiment of the use, the therapeutically effective amount is from about 0.01 mg per day to about 50.0 mg per day.

In an added embodiment of the use, the therapeutically effective amount is from about 0.1 mg per day to about 100.0 mg per day.

In still another embodiment of the use, the therapeutically effective amount is from about 0.1 mg per day to about 10.0 mg per day.

In an embodiment of the use, the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), . memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome.

In a further embodiment of the use, the neurological disease is depression. In one embodiment, the compound has the structure:



The subject invention thus discloses various derivatives and isomers of hydroxylated propargylamino indan and tetralin which have surprisingly varied potency and selectivity for MAO inhibition. The subject invention also provides modifications of the hydroxy compounds which have surprisingly varied MAO inhibitory properties depending upon the substitution pattern, however, the hydroxy compound is always a more potent inhibitor than the modified version. Thus, the modified version may be considered a prodrug of the more active hydroxy compound into which it will be metabolized *in vivo*.

In one embodiment of the invention, the prodrug compound is a carboxylic acid ester of the hydroxy compound. In another embodiment, the parent is a carbamate derivative of the hydroxy compound.

As discussed above, carbamate propargylamino indans and

tetralins have been reported in PCT International Application No. PCT/US97/24155 as both MAO inhibitors and AchE inhibitors. However, it is a further embodiment of this invention that such a prodrug compound will not be a potent inhibitor of AchE (IC_{50} >500 micromolar), and the IC_{50} for MAO-A inhibition of the corresponding hydroxy metabolite be at least 100 times more potent than the prodrug.

In one embodiment, the compounds are dihydroxy derivatives of propargylamino indan or tetralin. These derivatives are expected to be antioxidants, as well as MAO inhibitors. In another embodiment, the subject invention provides ester prodrugs.

Thus, the subject invention provides esters or carbamates of propargylamino indanols, propargylamino indandiols, propargylamino tetralinols or propargylamino tetralindiols, and may be prepared by methods of esterification or carbamoylation of hydroxy compounds. Ester derivatives (Figure 1) when R_2 equals hydrogen were prepared by reacting the propargylamino indanols with acyl chlorides in the presence of a strong organic acid such as trifluoroacetic acid or an acylation catalyst such as 4-dimethylaminopyridine (DMAP), with or without an inert organic solvent such as chloroform. Compounds when R_3 equals hydrogen were prepared either by direct acylation as described above, or by first N-protecting the amine moiety, e.g., by a tert-butoxycarbonyl (Boc) group, followed by acylation as above, and finally removing the protecting group. The preparation of compounds of the subject invention which are carbamates is described in PCT/US97/24155.

Propargylamino indanols may be prepared by reacting amino indanols with propargyl bromide in a polar organic solvent such as N,N-dimethylacetamide or acetonitrile in the presence of a base such as potassium carbonate. N-Methyl, N-propargylamino

indanols may be prepared by reductive alkylation of propargylamino indanols by methods known to those skilled in the art, e.g., with $NaCNBH_3$ and paraformaldehyde. Alternatively, N-methyl,N-propargylamino indanols were prepared by first methylating amino indanols either by $NaCNBH_3$/paraformaldehyde or by ethyl formate followed by $LiAlH_4$ reduction, and then reacting the N-methylamino indanols thus obtained with propargyl bromide as described above.

The N-propargyl derivatives of, *inter alia*, 3-amino-indan-4-ol, 1-amino-indan-4-ol, 3-amino-indan-5-ol and 7-amino-5,6,7,8-tetrahydro-naphthalen-2-ol were prepared.

Compounds of the subject invention with both R_1 and R_2 equal to $OCOR_4$ (see Figure 2, compound numbered 9) were prepared by propargylation of 5,6-di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8), as described above. 5,6-Di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8) was prepared from 5;6-bis-benzyloxy-1-indanone 3 as follows:

1) reductive amination of the compound numbered 3 in Figure 2 as described above gave 5,6-bis-benzyloxy-1-indanyl)methylamine (Figure 2, compound numbered 4);

2) the compound numbered 4 in Figure 2 was debenzylated by catalytic hydrogenation and protected by the Boc group to give N-Boc-1-methylamino-indan-5,6-diol (Figure 2, compound numbered 6); and

3) Compound 6 in Figure 2 was esterified as described above and the protecting group removed as previously described to give 5,6-di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8).

The diester tetralin derivative numbered 12 (Figure 3) was prepared by esterification of the dihydroxy tetralin numbered 11 (Figure 3).

Table 1. Chemical Data

cmpd #	ster	R_2	R_1	R_1 pos	R_3	n	m	mp	formula	yield (%)
100*	S	H	OH	6	H	0	1	175-7	$C_{13}H_{17}NO_4S$	45
101*	R	H	OH	6	H	0	1	173-5	$C_{13}H_{17}NO_4S$	42
102	S	H	OCOMe	6	H	0	1	138-40	$C_{14}H_{16}ClNO_2$	46
103	R	H	OCOMe	6	H	0	1	156-8	$C_{14}H_{16}ClNO_2$	77
104	S	H	OCOtBu	6	H	0	1	126-8	$C_{17}H_{22}ClNO_2$	67
105	R	H	OCOtBu	6	H	0	1	128-30	$C_{17}H_{22}ClNO_2$	46
106	S	H	OCOnBu	6	H	0	1	149-50	$C_{17}H_{22}ClNO_2$	37
107	R	H	OCOnBu	6	H	0	1	155-7	$C_{17}H_{22}ClNO_2$	85
108	S	H	$OCOCH_2Ph$	6	H	0	1	144-5	$C_{20}H_{20}ClNO_2$	22
109	R	H	$OCOCH_2Ph$	6	H	0	1	145-7	$C_{20}H_{20}ClNO_2$	52
110	S	H	OCOPh	6	H	0	1	202-4	$C_{19}H_{18}ClNO_2$	18
111	R	H	OCOPh	6	H	0	1	210-11	$C_{19}H_{18}ClNO_2$	61
112	rac	H	OH	6	Me	0	1	210-11	$C_{13}H_{16}ClNO$	70
113	S	H	OH	6	Me	0	1	82-4	$C_{13}H_{16}ClNO$	72
114	R	H	OH	6	Me	0	1	71-2	$C_{13}H_{16}ClNO$	78
115	S	H	OCOMe	6	Me	0	1	168-70	$C_{15}H_{18}ClNO_2$	95
116	R	H	OCOMe	6	Me	0	1	168-70	$C_{15}H_{18}ClNO_2$	93
117	rac	H	OH	4	Me	0	1	160-62	$C_{13}H_{16}NClO$	89
118	rac	H	OH	7	Me	0	1	83-5	$C_{13}H_{16}NClO$	53
119	rac	H	OCOMe	4	Me	0	1	148-50	$C_{15}H_{18}ClNO_2$	72
120	rac	H	OCOPh	4	Me	0	1	176-8	$C_{20}H_{20}ClNO_2$	59
121	rac	H	$OCOPh(OMe)_2$	4	Me	0	1	183-5	$C_{22}H_{24}ClNO_4$	39
122	rac	H	OCOPh	7	Me	0	1	185-7	$C_{20}H_{20}ClNO_2$	45
123	rac	H	OH	7	Me	1	1	220-1	$C_{14}H_{18}NClO$	66
124	rac	H	OCOPh	7	Me	1	1	104-6	$C_{21}H_{22}ClNO_2$	71
125	S	H	OCOnBu	6	Me	0	1	78-80	$C_{18}H_{24}ClNO_2$	73
126	R	H	OCOnBu	6	Me	0	1	96-8	$C_{18}H_{24}ClNO_2$	72
127	S	H	OCOPh	6	Me	0	1	73-5	$C_{20}H_{20}ClNO_2$	52
128	R	H	OCOPh	6	Me	0	1	82-4	$C_{20}H_{20}ClNO_2$	56

Table 1. Chemical Data cont.

129	S	H	OCOtBu	6	Me	0	1	153-5	$C_{18}H_{24}ClNO_2$	73
130	R	H	OCOtBu	6	Me	0	1	155-7	$C_{18}H_{24}ClNO_2$	78
131	S	H	OCOPh(Me)	6	Me	0	1	**	$C_{21}H_{22}ClNO_2$	51
132	R	H	OCOPh(Me)	6	Me	0	1	82-4	$C_{21}H_{22}ClNO_2$	46
133	S	H	$OCOPh(OMe)_2$	6	Me	0	1	118-20	$C_{22}H_{24}ClNO_2$	58
134	R	H	$OCOPh(OMe)_2$	6	Me	0	1	73-5	$C_{22}H_{24}ClNO_2$	68
135	rac	H	OH	7	H	0	1	166-8	$C_{12}H_{14}ClNO$	35
136	rac	H	OH	4	H	0	1	196-8	$C_{12}H_{14}ClNO$	66
137	rac	OCOPh (5-pos)	OCOPh	6	Me	0	1	114-5	$C_{27}H_{24}ClNO_4$	59
138	rac	OCOPh (6-pos)	OCOPh	7	Me	1	1	180-2	$C_{28}H_{26}ClNO_4$	58

ster = stereochemistry
pos = position
* mesylate salts
** wide range, hygroscopic

Table 2. ^{1}H-NMR Data (R_1 = R_3 = H) (300 MHz, dimethyl sulfoxide (DMSO)-d_6)

Cmpd #	Ph	indan			Pg		R_4	NH_2
		C3-H	C2-H	C1-H	CH2	CH		
102 103	7.52(d) 7.35(d) 7.10(dd)	4.79(m)	2.43(m) 2.28(m)	2.83(m) 3.12(m)	3.88(m)	3.71(m)	2.27 (Me,s)	10.2 (br s)
104 105	7.48(d) 7.36(d) 7.07(dd)	4.79(m)	2.45(m) 2.27(m)	2.85(m) 3.12(m)	3.90(m)	3.72(m)	1.30 (tBu,s)	10.15 (br s)
108 109	7.48(d) 7.36(d) 7.07(dd)	4.80(m)	2.45(m) 2.28(m)	2.85(m) 3.13(m)	3.91(m)	3.72(m)	7.38(m,1H) 7.33(m,4H) 3.99(CH2,s)	10.2 (br s)
106 107	7.48(d) 7.35(d) 7.08(dd)	4.79(m)	2.45(m) 2.26(m)	2.85(m) 3.11(m)	3.90(m)	3.71(m)	2.57(t,2H) 1.61(m,2H) 1.38(m,2H) 0.91(t,3H)	10.1 (br s)
110 111	7.67(d) 7.42(d) 7.28(dd)	4.83(m)	2.46(m) 2.30(m)	2.86(m) 3.16(m)	3.93(m)	3.72(m)	8.13(d,2H) 7.76(t,1H) 7.61(t,2H)	10.15 (d)

Table 3. ^{1}H-NMR Data (R_1 = H, R_3 = Me)(300 MHz, D_2O)

Cmpd #	Ph	Indan			Propargyl		R_4	N-Me
		C3-H	C2-H	C1-H	CH_2	CH		
116 115	7.50(d) 7.35(d) 7.25(dd)	5.22(m)	2.46(m) 2.60(m)	3.07(m) 3.17(m)	4.05(m)	3.15(m)	2.37(Me,s)	2.83(s)
126 125	7.50(d) 7.33(d) 7.22(dd)	5.23(m)	2.49(m) 2.62(m)	3.07(m) 3.17(m)	4.05(m)	3.17(m)	2.69(t,2H) 1.73(m,2H) 1.44(m,2H) 0.97(t,3H)	2.82(s)
128 127	7.50(d) 7.40(d) 7.29(dd)	5.17(m)	2.57(m) 2.47(m)	3.06(m) 3.17(m)	4.00(m)	3.15(m)	8.11(dd,2H) 7.74(dt,1H) 7.57(t,2H)	2.81(s)
129 130	7.49(d) 7.28(d) 7.21(dd)	5.20(m)	2.60(m) 2.45(m)	3.05(m) 3.16(m)	4.03(m)	3.17(m)	1.37(s,9H)	2.81(s)
131 132	7.90(d,1H) 7.44(t,1H) 7.36(m,2H) 7.21(m,2H) 7.08 (dd,1H)	5.02(m)	2.50(m) 2.40(m)	3.08(m) 2.95(m)	3.93(m)	3.14(m)	For Ar H's, see under Ph. 2.43(s,Me)	2.72(s)
133 134	7.5-7.1 (m,4H) 6.74(dd,2H)	5.05 (br d)	2.50(m) 2.41(m)	3.08(m) 2.95(m)	3.92(m)	3.16(m)	For Ar H's, see under Ph. 3.84 (s,6H, OMe)	2.73(s)

Table 3. ^{1}H-NMR Data (R_1 = H, R_3 = Me)(300 MHz,D_2O) cont.

120 *	7.62(t,1H) 7.44(t,1H) 7.35(d,1H)	5.19(m)	2.46(m)	2.98(m) 2.80(m)	4.09(m)	3.84(s)	8.13(d,2H) 7.77(t,2H) 7.62(t,1H)	
119	7.50(m,2H) 7.26(d,1H)	5.29(dd)	2.60(m) 2.47(m)	2.97(m)	4.05(m)	3.15(m)	2.39(s,3H)	2.81(s)
121	7.46(t,2H) 7.23(dd, 1H)	5.15 (br d)	2.46(m)	2.93(m)	3.97(m)	3.16(m)	7.42(t,1H) 6.75(d,2H) 3.83(s,6H, OMe)	2.73(s)
122 *	7.50(t,1H) 7.35(d,1H) 7.25(d,1H)	5.18 (br s) 4.96 (br s)	2.95(m) 2.36(m)	3.50(m)	4.40- 3.90(m)	3.80(m)	8.20(dd,2H) 7.78(t,1H) 7.61(t,2H)	2.68(s) 2.56(s)

* DMSO-d6

Table 4. ^{1}H-NMR Data (R_1 or R_2=OH)
(300MHz, D_2O)

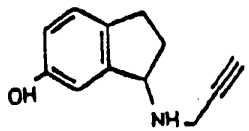
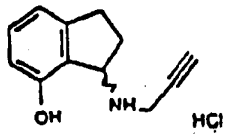
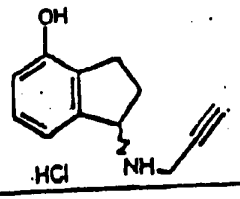
Cmpd #	structure	Ph	indan			propargyl		N-Me
			C3-H	C2-H	C1-H	CH_2	CH	
100 101	 mesylate	7.32 (d) 7.04 (d) 6.98 (dd)	4.93 (dd)	2,59 (m) 2.30 (m)	3.06 (m) 2.96 (m)	3.99 (m)	3.06 (m)	
135		7.35 (t) 9.98 (d) 6.98 (d)	5.07 (dd)	2,57 (m) 2.30 (m)	3.16 (m) 3.01 (m)	4.01 (m)	3.00 (m)	
136		7.30 (d) 7.16 (d) 6.98 (d)	4.99 (dd)	2.60 (m) 2,32 (m)	3.06 (m) 2.96 (m)	4.02 (m)	3.06 (m)	

Table 4. ^{1}H-NMR Data (R_1 or R_1=OH) cont.
(300MHz, D_2O)

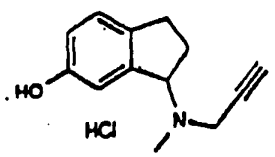
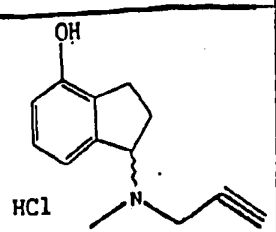
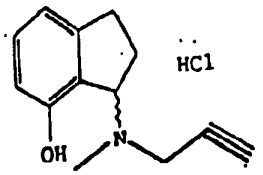
Cmpd #	structure	Ph	indan			propargyl		N-Me
			C3-H	C2-H	C1-H	CH_2	CH	
113 114		7.30 (d) 7.00 (m,2H)	5.1 (dd)	2.52 (m) 2.41 (m)	3.05 (m) 2.95 (m)	4.00 (m)	3.13 (m)	2.78 (s)
117		7.21 (t) 7.03 (d) 6.87 (d)	5.09 (dd)	2.40 (m) 2.30 (m)	2.85 (m)	3.90 (m)	3.02 (s)	2.65 (s)
118		7.35 (t) 6.97 (d) 6.82 (d)	5.30 (dd)	2.50 (m) 2.39 (m)	3.10 (m) 2.95 (m)	4.06 (m)	3.10 (s)	2.79 (s)

Table 5. MAO in vitro Data

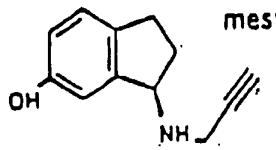
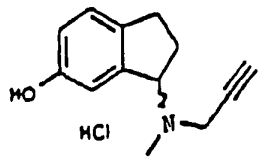
Cmpd#		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
101	R		0.3	0.23	1.3
100	S		500	300	1.66
112			0.03	0.01	3.0
114	R		0.01	0.03	0.33
113	S		12	23	0.52

Table 5. MAO in vitro Data cont. 1

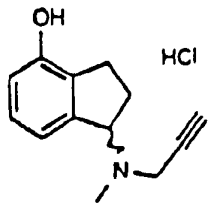
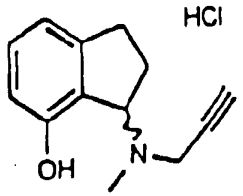
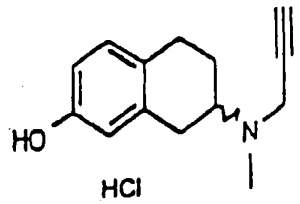
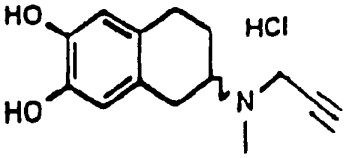
Cmpd#		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
117			0.0083	0.07	0.1
118			0.07	0.05	1.4
123			0.41	0.48	0.85
139			4.5	41	0.11

Table 5. MAO in vitro Data cont. 2

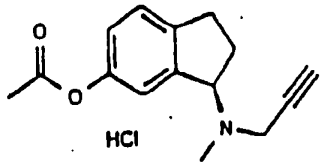
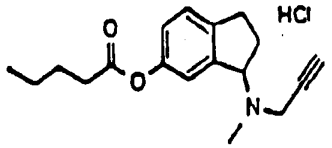
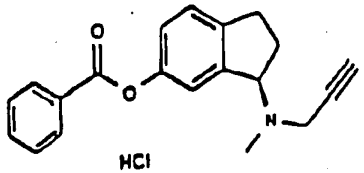
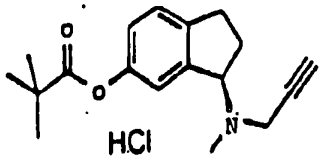
Cmpd #		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
116			0.035	0.0056	6.25
126			0.058	0.13	0.45
128	R		0.2	1.0	0.2
127	S		3.8	5.6	0.68
130	R		0.56	2.5	0.22

Table 5. MAO in vitro Data cont. 3

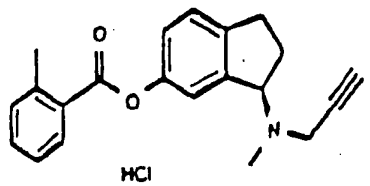
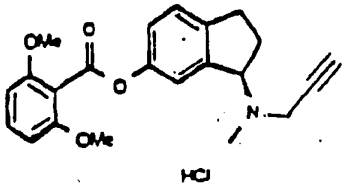
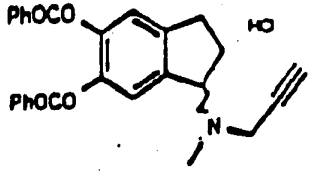
Cmpd#		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
129	S		2.5	17	0.15
132			1.1	9.9	0.11
134			1.2	5.9	0.20
137			1.4	21.0	0.07

Table 5. MAO in vitro Data cont. 4

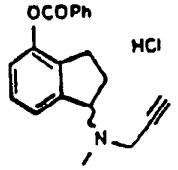
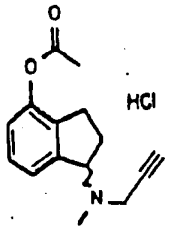
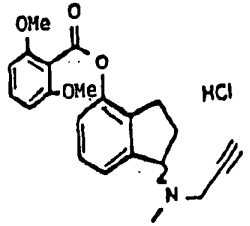
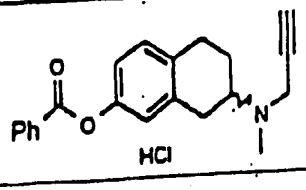
Cmpd #		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
120			0.13	0.91	0.14
119			0.018	0.11	0.16
121			0.34	3	0.11
124			1.2	1.2	1

Table 5. MAO in vitro Data cont. 5

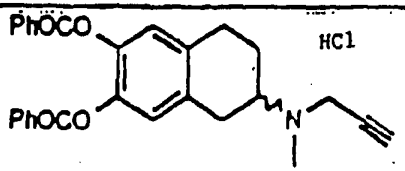
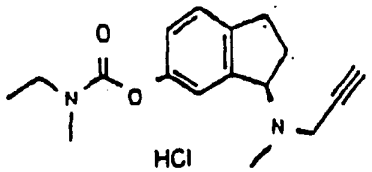
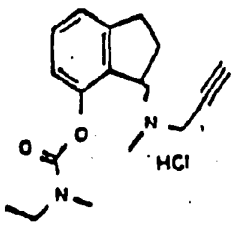
Cmpd#		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
138			1.2	0.4	3
140			4.3	12	0.36
141			65	100	0.65

Table 5. MAO in vitro Data cont. 6

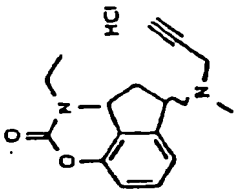
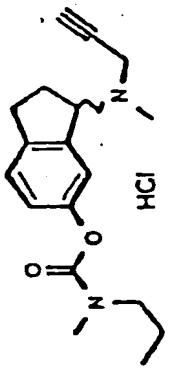
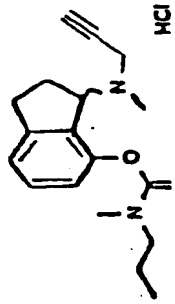
Cmpd #		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
142			0.027	4	0.007
143			5.6	9.2	0.61
144			71	63	1.1

Table 5. MAO in vitro Data cont. 7

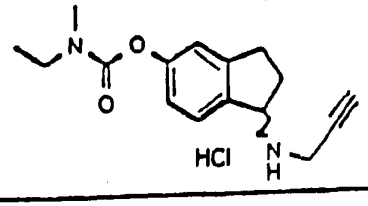
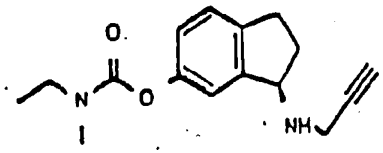
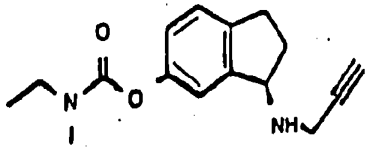
Cmpd#		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
145			???	???	
146		 tartrate	300	> 1000	< 0.3
147		 HCl	550	> 1000	< 0.55

Table 5. MAO in vitro Data cont. 8

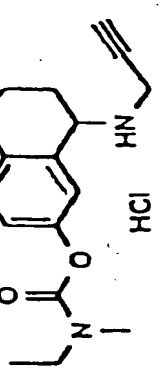
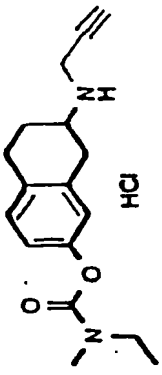
Cmpd #		Structure	In vitro $IC_{50}(\mu M)$		
			A	B	A/B
148			500	100	5
149			2	100	0.02

Table 6. MAO in vivo Data

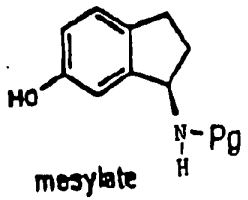
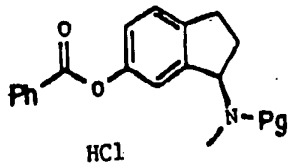
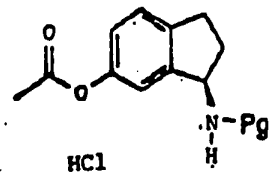
Cmpd #	structure	dose			% inhibition	
		mg/kg	µmol/kg	days	A	B
101	 mesylate	5	18	10	35	47
		25	88	10	57	65
128	 HCl	1	2.9	7	87	77
		5	15	7	95	91
		15	44	7	98	91
103	 HCl	5	18.7	10	21	32
		25	94	10	64	77

Table 6. MAO in vivo Data cont 1.

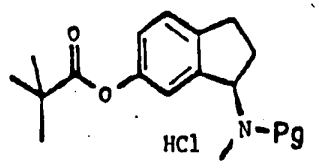
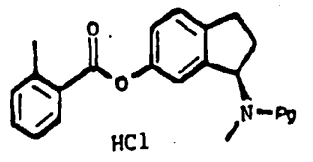
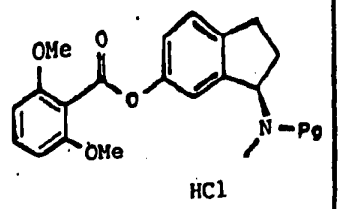
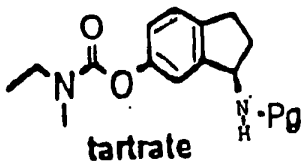
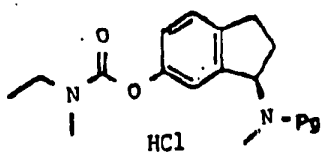
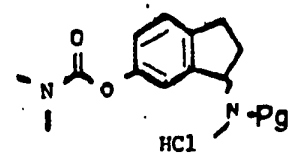
Cmpd #	structure	dose			% inhibition	
		mg/kg	µmol/kg	days	A	B
130		3.2	10	acute	24	22
132		3.6	10	acute	41	37
134		4	10	acute	9	0

Table 6. MAO in vivo Data cont 2.

Cmpd #	structure	dose			% inhibition	
		mg/kg	µmol/kg	days	A	B
146	 tartrate	17 52	50 100 150	7 5 7	46 56 74	52 74 87
140	 HCl	0.64 3.2 16.1	2 10 50	5 5 5	6 51 65	10 30 73
150	 HCl	0.62 3.1 15.4	2 10 50	5 5 5	7 25 80	-5 14 73

Experimental Details

EXAMPLE 1: GENERAL PROCEDURE FOR PROPYN-2-YLAMINO (PROPARGYLAMINO) INDANOLS (R_3 = H)

A mixture of amino indanol(35 mmol), propargyl bromide (35 mmol) and potassium carbonate (35 mmol) in DMA (100 ml) was stirred at room temperature (RT) for 24 hours. The reaction mixture was filtered, diluted with water (200 ml) and extracted with toluene (4 x 100 ml). The organic extracts were combined, dried and evaporated to dryness under reduced pressure. The residue was then subjected to flash column chromatography (hexane : EtOAc, 1:1). The free base was optionally converted to an acid addition salt.

Alternatively, the propargylation reaction was run in acetonitrile at elevated temperature, e.g., 60°C for 4 hours. The reaction mixture was then filtered, and the cake washed with acetonitrile. The combined layers were evaporated to dryness, and the residue (brown oil) subjected to flash column chromatography (hexane : EtOAc, 2:1). The product (white solid) was thus obtained in 40 - 55 % yield.

Thus were prepared: (R)-3-prop-2-ynylamino-5-indanol mesylate, (S)-3-prop-2-ynylamino-5-indanol mesylate, 1-prop-2-ynylamino-4-indanol HCl, and 3-prop-2-ynylamino-4-indanol HCl.

EXAMPLE 2: GENERAL PROCEDURES FOR N-METHYL-PROP-2-YNYLAMINO INDANOLS (R_3=Me), EXEMPLIFIED BY 3-(METHYL-PROP-2-YNYL AMINO)-5-INDANOL

Experiment 2A

A mixture of (S)-3-prop-2-ynylamino-5-indanol (5.0 g, 26.7 mmol), paraformaldehyde (3.6 g, 30 mmol) and $NaCNBH_3$ (1.96 g, 31.2 mmol) in abs MeOH (90 ml) was refluxed under argon for 4 hours. The crude product obtained after evaporation of the solvent was purified by flash chromatography (hexane: EtOAc, 70:30) and was converted to its HCl salt (etheral HCl: 4.2g(17.6 mmol, 66%)). ^{1}H NMR (DMSO-d_6):11.7(br d,NH), 9.62(br s, OH), 6.8-7.3(3H), 4.98(m,1H), 3.98(ABq,2H), 3.0(m,1H), 2.90(m,1H), 2.77(s,Me), 2.48(m1H), 2.40(m,1H)ppm.
^{1}H NMR(D_2O):7.29(d,1H),6.95-7.02(2H),5.09(m,1H),4.0(AB q, 2H), 3.0(m,1H),2.90(m,1H),2.77(s,Me),2.48(m,1H),2.40(m,1H)ppm.

Thus were prepared (R)3-(methyl-prop-2-ynylamino)-5-indanol and 1-(methyl-prop-2-ynylamino)-4-indanol.

Example 2B: 3-(methyl-prop-2-ynylamino)-4-indanol

Experiment 2B1

3-amino-4-indanol (3.70 g, 24.8 mmol) in ethylformate (200 ml) was refluxed for 18 hr. The solvent was then removed under reduced pressure, and the residue was purifed by flash chromatography to give 4.10 g (93%) of N-(7-hydroxy-indan-1-yl)-formamide as a yellow solid.

Experiment 2B2

Lithium aluminium hydride (4.5 g) was added portionwise to stirred and cooled dry THF (100 ml) at 0°C. A solution of N-(7-hydroxy-indan-1-yl)-formamide (4.1 g) in dry THF (70 ml) was

added while maintaining the temperature at 5-10°C. The reaction mixture was stirred at ambient temperature for 9 hr, cooled and treated with water (100 ml). The pH was adjusted to 8-9, water (200 ml) was added, and the mixture was extracted with ether (6 X 300 ml). The etheral extract was evaporated to dryness to give 3.2 g (94%).

Experiment 2B3

3-Methylamino-4-indanol was reacted with propargyl bromide in acetonitrile as described in Example 1.

Example 2C

7-(methyl-prop-2-ynylamino)-2-tetralinol and 6-(methyl-prop-2-ynylamino)-2,3-tetralindiol were prepared according to Chumpradit et al. and Horn et al.

EXAMPLE 3: GENERAL PROCEDURE FOR ESTERIFICATION OF PROP-2-YNYL AMINO INDANOLS AND TERALINOLS, EXEMPLIFIED BY PENTANOIC ACID (R)-3-PROP-2-YNYLAMINO-INDAN-5-YL ESTER HCL (Cmpd # 107)

To a solution of (R)3-prop-2-ynylamino-5-indanol (2.5 g, 13.4 mmol) in $CHCl_3$(30ml) and TFA (5 ml), was added valeryl chloride (2.03 g, 2.0 ml, 16.7 mmol). The solution was heated at 60° for 8 hours and cooled to RT. Water (250 ml) was added, and the pH adjusted to 7 by means of concentrated aqueous ammonia. Extracted with methylene chloride (4x100 ml), dried and evaporated to dryness under reduced pressure. The residue (brown oil, 3.65 g) was purified by flash chromatography (SiO_2, CH_2Cl_2:MeOH 99:1). The free base thus obtained (3.25 g) was dissolved in dry ether (80 ml), and 20% etheral HCl was added. The resulting suspension was stirred for 2 hours at RT, the solid product was collected by filtration and washed with ether (20 ml) and dried at 60° to give 3.45 g (11.2 mmol, 85%) of the ester HCl.

EXAMPLE 4: ALTERNATIVE PROCEDURE, EXEMPLIFIED BY BENZOIC ACID (R)-3-PROP-2-YNYLAMINO-INDAN-5-YL ESTER (Cmpd # 111)

(R) 3-prop-2-ynylamino-5-indanol (3.0 g, 16 mmol) was dissolved in dry THF (75 ml), and triethylamine (3.15 ml, 22.6 mmol) followed by Boc_2O (4.5 g, 20.6 mmol) was added. The solution was stirred at RT for 24 hours and evaporated to dryness. The residue was taken up in water (200 ml) and extracted with CH_2Cl_2 (4x100 ml). The organic layers were combined, dried and evaporated to dryness. The crude product was purified by flash column chromatography (hexane: EtOAc 3:1) to give 3.75 g (81.5%) of a white solid.
^1H NMR (DMSO-d6) (a 1:1 mixture of 2 rotamers): 9.17(s,OH), 7.0 (d,1H), 6.62 (dd, 1H), 6.5(br s, 1H), 5.51 & 5.22 (brs, 1H), 4.05, 3.72, 3.60, 3.38(m,2H), 3.06(br s, 1H), 2.83 (m,1H), 2.64(m,1H),2.30(br s, 1H, 2.10(br s, 1H), 1.4 & 1.27 (2s,9H)ppm.

(R) N-Boc 3-prop-2-ynylamino-5-indanol (2.65 g, 9.23 mmol) was dissolved in dry methylene chloride (20 ml), and triethylamine (2.65 ml, 18.5, mmol), DMAP (0.11 g, 0.9 mmol) and benzoyl chloride (1.7 ml, 18.5 mmol) was added. The solution was stirred at RT for 3 hours, water (100 ml) was added and acidified to pH 4 (aq HCl). The organic layer was separated and washed with 10% HCl. The aqueous layer was washed with methylene chloride (100 ml), and the combined organic phases were dried and evaporated to dryness in vacuo. The crude product (5.2 g brown oil) was purified by flash column chromatography (hexane: EtOAc 3:1) to give 4.1 g (90%) of a white solid.

(R) N-Boc-3-prop-2-ynylamino-5-benzoyloxy indan (2.55 g, 6.5 mmol) was dissolved in dioxan (25 ml), and HCl/dioxan (25 ml) was added. The mixture was stirred at RT for 4 hours and the solvent was evaporated to dryness in vacuo. Ether (50 ml) was added, the suspension was then stirred at RT for 2 hours. The

solid was collected by filtration, washed with ether and dried (1.5 g). The crude product was crystallized from iPrOH (90 ml) to give 1.3 g (3.96 mmol, 61%), mp 210-2°C.

EXAMPLE 5: PREPARATION OF BENZOIC ACID (S)-3-(METHYL-PROP-2-YNYL-AMINO)-INDAN-5-YL ESTER HCL Cmpd # 127

(S)3-(methyl-prop-2-ynylamino)-5-indanol (1.5 g, 7.46 mmol) was dissolved in dry methylene chloride (15 ml), and triethylamine (2.15 ml, 15.5 mmol), DMAP (0.08 g, 0.66 mmol) and benzoyl chloride (2.1 ml, 18.1 mmol) was added. The solution was stirred at RT for 2 hours, water (100 ml) was added and acidified to pH 4 (aq HCl). The organic layer was separated, washed with 10% HCl. The aqueous layer was washed with methylene chloride (4x100 ml), and the combined organic phases were dried evaporated to dryness in vacuo. The crude product (3.78 g brown oil) was purified by flash column chromatography (hexane: EtOAc 4:1) to give 1.6 g (5.3 mmol, 71%) of a yellow oil. The free base was converted to the HCl salt (etheral HCl, 2 hours, RT), 1.39g (4.07 mmol, 77%, 55% from the hydroxy compound).

By the same procedure was prepared 7-O-benzoyl-2-(methyl-prop-2-ynylamino)-tetralin Hcl; ^{1}HNMR (D_2O): 7.20, 6.98, 6.95 (3H, ArOCO), 8.05, 7.71, 7.53 (5H, PhCOO), 4.15 (m, 2H, $\underline{CH_2}CCH$), 3.80 (m, 1H, C_7-H), 3.15 (t, 1H, $CH_2C\underline{CH}$), 3.14, 3.01 (m, 2H, C_8-H), 2.8-3.0 (m, 2H, C_5-H), 2.31, 1.87 (m, 2H, C_6-H), 3.0 (S, 3H, Me) ppm.

The same procedure was also used to prepare 6,7-di-O-benzoyl-2-(methyl-prop-2-ynylamino)-tetralin HCl, ^{1}HNMR (DM80-d_6): 7.91 (dd, 4H), 7.65 (t,2H), 7.46 (t,4H), 7.28 (s, 2H), 4.24 (br s, 2H), 3.87 (br s, 1H), 3.74 (m, 1H), 3.35-2.90 (m, 4H), 2.87 (s, 3H), 2.39 (m, 1H), 1.90 (m, 1H) ppm.

EXAMPLE 6: PREPARATION OF 5,6-DI-O-BENZOYL-1-(METHYL-PROP-2-YNYL-AMINO)-INDAN HCL Cmpd # 137):

Experiment 6A: (5,6-Bis-benzyloxy-1-indan-1-yl)-methylamine HCl (Figure 2, Compound 4)

A mixture of 5,6-dibenzyloxy-1-indanone (10.0 g, 29 mmol), 8M ethanolic methylamine (30 ml, 240 mmol), methylamine HCl (7.15 g, 106 mmol), and $NaCNBH_3$ (2.95 g, 47 mmol) in dry THF (750 ml) and methanol (250 ml) was refluxed under nitrogen for 4 hours. The reaction mixture was cooled to 5°C, acidified with concentrated HCl to pH 1.5, and evaporated to dryness. The solid residue was treated with a mixture of methylene chloride (600 ml) and water (400 ml). The aqueous layer was separated, extracted with methylene chloride (4x100 ml), and the combined organic layers were evaporated to dryness. The crude product thus obtained was slurried in EtOAc (80 ml) for 30 min at RT, filtered and purified by flash column chromatography (CH_2Cl_2 : MeOH, 80:20), to give 6.3 g (54.8 %), mp: 180-182°C.

Experiment 6B: 1- Methylamino -1-indan- 5,6-diol HCl (Figure 2, Compound 5)

A solution of (5,6-bis-benzyloxy-1-indan-1-yl)-methylamine HCl (3.15 g, 7.96 mmol) in MeOH (250 ml) was hydrogenated (44 psi) over 10% Pd/C (1.05 g) at RT for 3 hours. The mixture was filtered (Filteraid), and the filtrate evaporated to dryness. The residue was treated with charcoal in boiling MeOH, filtered and evaporated to dryness, to give 1.6 g of a light grey solid, mp : 153-5°C.

^1H NMR (DM80-d_6): 9.3-8.8 (3H, br m, OH, NH_2), 7.02 (s, 1H, Ar), 6.08 (s, 1H, Ar), 4.7 (dd, 1H, C_3-H), 2.92 (m, 1H, C_1-H), 2.66 (m, 1H, C_1-H), 2.44 (s, 3H, Me), 2.33 (m, 1H, C_2-H), 2.11 (m, 1H, C_2-H') ppm.

Experiment 6C: N-Boc-1- methylamino -1-indan- 5,6-diol (Figure 2, Compound 6)

To a solution of 1-methylamino-1-indan-5,6-diol HCl (0.5 g, 2.32 mmol) in water (30 ml) was added dioxane (30 ml), $NaHCO_3$ (0.6 g) and Boc_2O (0.6 g). The reaction mixture was stirred at RT for 4 hours under nitrogen, evaporated to dryness, and the solid residue taken up in a mixture of water (100 ml) and methylene chloride (100 ml). The aqueous layer was separated and extracted with methylene chloride (5x50 ml). The latter was filtered, washed with water, dried and evaporated to dryness to give a viscous oil which was purified by flash column chromatography (CH_2Cl_2 : MeOH, 95:5) to give 0.35 g (54 %) of a viscous oil which soon solidified.

Experiment 6D: N-Boc-(5,6-di-O-benzoyl-1-indan-1-yl)-methylamine (Figure 2, Compound 7)

To a solution of N-Boc-1-methylamino-1-indan-5,6-diol (0.34 g, 1.22 mmol) in methylene chloride (15 ml) was added triethylamine (0.49 g, 4.88 mmol), DMAP (0.03 g, 0.244 mmol) and benzoyl chloride (0.69 g, 4.88 mmol), and the solution was stirred at RT for 4.5 hours. Water (100 ml) was added, acidified to pH 4 with dilute HCl. The organic layer was separated and washed with 10% HCl. The aqueous layer was extracted with methylene chloride (2x75 ml), and the latter was washed with 10% HCl. The combined organic layers were dried, evaporated to dryness, and the residue purified by flash column chromatography (hexane : EtOAc, 50:50) to give 0.50 g (40%) of a yellow oil.

Experiment 6E: (5,6-di-O-Benzoyl-1-indan-1-yl)-methylamine HCl (Figure 2, Compound 8)

To a solution of N-Boc-(5,6-di-O-benzoyl-1-indan-1-yl)-methylamine (0.29 g, 0.59 mmol) in dioxane (5 ml) was added 20% HCl in dioxane (5 ml), and the mixture stirred at RT for 4 hours under nitrogen. The solvent was removed and ether (40 ml) was added to the residue, and the suspension stirred at RT for 1 hour. The solvent was removed to give 0.11 g (89 %) of a white solid, mp : 192-3°C.

^{1}H NMR ($CDCl_3$): 8.1-7.2 (12H, Ar), 4.79 (br s, 1H, C_3-H), 3.40 (m, 1H, C_1-H), 3.01 (m,1H,C_1-H), 2.60 (s, 3H, Me), 2.50 (m, 1H, C_2-H), 1.83 (m, 1H, C_2-H') ppm.

Experiment 6F: 5,6-di-O-Benzoyl-1-(methyl-prop-2-ynyl-amino)-indan HCl (Figure 2, Compound 9 (Cmpd # 137))

To a solution of (5,6-di-O-benzoyl-1-indan-1-yl)-methylamine HCl (~0.2 g, 0.48 mmol) in acetonitrile (100 ml) was added K_2CO_3 (130 mg, 0.96 mmol), followed after 15 min by a solution of propargyl bromide (56 mg, 0.48 mmol) in acetonitrile (10 ml). The reaction mixture was stirred under nitrogen at RT for 20 hours, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (hexane : EtOAc, 50:50) to give 0.15 g (0.35 mmol, 75 %) of a viscous light tan oil.

The free base was dissolved in MeOH (30 ml), and saturated etheral HCl (4 ml) was added. The solution was stirred at RT for 30 min and evaporated to dryness. The oily residue was triturated three times in ether, to give 120 mg (0.26 mmol, 74%) of a light tan solid.

NMR ($CDCl_3$): 8.1 - 7.2 (m, 12H, Ar), 5.1 (br d, 1H, C1-H), 3.91 (br s, 2H, $\underline{CH_2}CCH$), 3.6 - 2.5 (m, 8H, indan CH_2's, Me, $CH_2C\underline{CH}$).

EXAMPLE 7: INHIBITION OF MAO ACTIVITY IN VITRO

EXPERIMENTAL PROTOCOL

The MAO enzyme source was a homogenate of rat brain in 0.3 M sucrose 1:20 w/v. The homogenate was pre-incubated with serial dilutions of the test compounds (Table 5) for 60 minutes at 37°C. ^{14}C-labeled substrates (2-phenylethylamine, hereinafter PEA; 5-hydroxytryptamine, hereinafter 5-HT) were then added, and the incubation continued for a further 20 minutes (PEA), or 30-45 minutes (5-HT). In the case of PEA, the enzyme concentration was chosen so that not more than 10% of the substrate was metabolized during the course of the reaction. The reaction was then stopped by addition of citric acid. Radioactivity indicates the production of 5-HT and PEA metabolites formed as a result of MAO activity. Activity of MAO in the sample was expressed as a percentage of control activity in the absence of test compounds after subtraction of appropriate blank values. The activity determined using PEA as substrate is referred to as MAO-B, and that determined using 5-HT as MAO-A.

EXAMPLE 8: INHIBITION OF MAO ACTIVITY IN VIVO: CHRONIC TREATMENT EXPERIMENTAL PROTOCOL

Rats were treated with the test compounds (Table 5) at several dose levels by oral administration, one dose daily for 7-21 days, and decapitated 2 hours after the last dose. The activities of MAO-A and MAO-B were determined in the brain, liver and intestine as described in the previous example. Inhibition of MAO activity was calculated by dividing MAO activity in the treated rats by MAO activity in the control rats (saline treated, MAO activity in these rats was taken as 100%).

A mixture of toluene: ethyl acetate (1:1) was added to the reaction and mixed for 10 minutes, followed by 5 minutes of centrifugation at 1760 g. The upper phase was taken for radioactive determination by liquid scintillation spectrometry.

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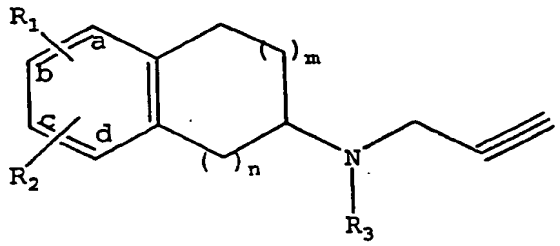
What is claimed is:

1. A compound having the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

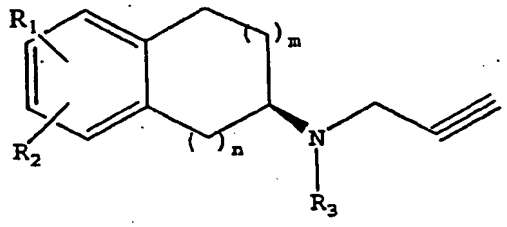
wherein n is 0 or 1; and

wherein m is 1 or 2,

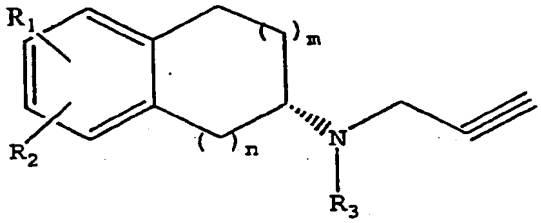
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

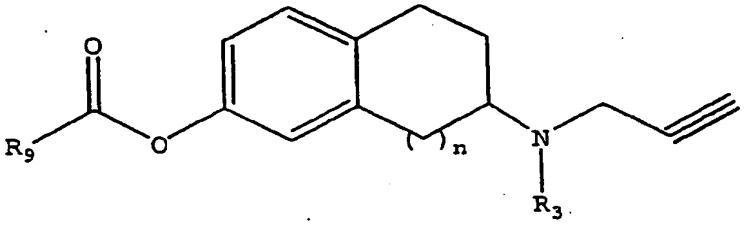
3. The compound of claim 1 having the structure:



4. The compound of claim 1 having the structure:

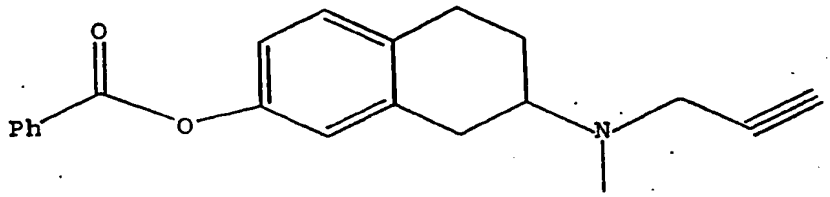


5. The compound of claim 1 having the structure:



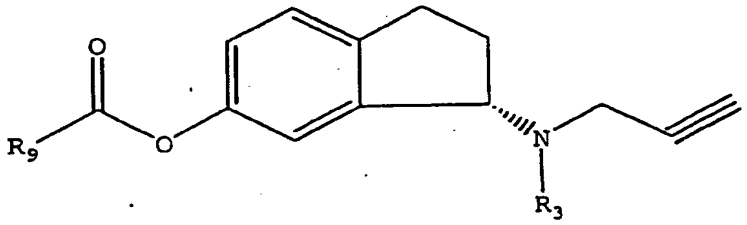
6. The compound of claim 5, wherein n is 1.

7. The compound of claim 6 having the structure:

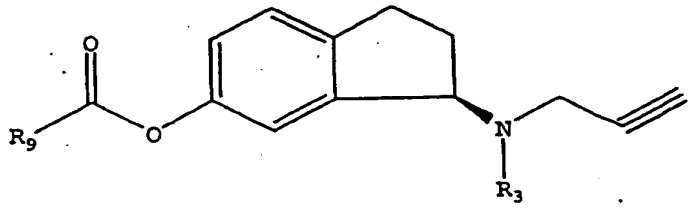


8. The compound of claim 5, wherein n is 0.

9. The compound of claim 8 having the structure:



10. The compound of claim 8 having the structure:



11. The compound of claim 8, wherein R_9 is Me and R_3 is H.

12. The compound of claim 8, wherein R_9 is tBu and R_3 is H.

13. The compound of claim 8, wherein R_9 is nBu and R_3 is H.

14. The compound of claim 8, wherein R_9 is CH_2Ph and R_3 is H.

15. The compound of claim 8, wherein R_9 is Ph and R_3 is H.

16. The compound of claim 8, wherein R_9 is Me and R_3 is Me.

17. The compound of claim 8, wherein R_9 is nBu and R_3 is Me.

18. The compound of claim 8, wherein R_9 is Ph and R_3 is Me.

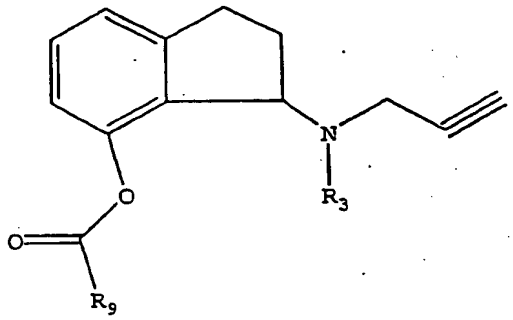
19. The compound of claim 8, wherein R_9 is tBu and R_3 is Me.

20. The compound of claim 8, wherein R_9 is Ph(Me) and R_3 is Me.

21. The compound of claim 8, wherein R_9 is $Ph(OMe)_2$ and R_3 is Me.

22. The compound of claim 8, wherein R_9 is $Ph(OMe)_2$ and R_3 is H.

23. The compound of claim 1 having the structure:

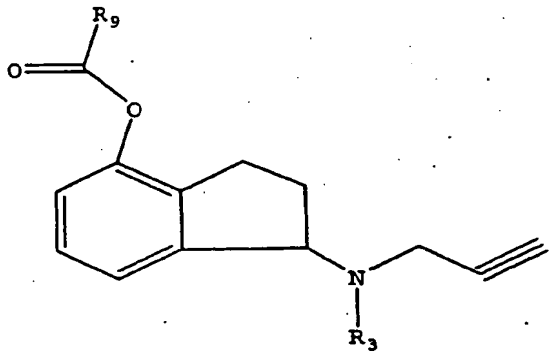


24. The compound of claim 23, wherein R_3 is Me and R_9 is Me.

25. The compound of claim 23, wherein R_3 is Me and R_9 is Ph.

26. The compound of claim 23, wherein R_3 is Me and R_9 is $Ph(OMe)_2$.

27. The compound of claim 1 having the structure:

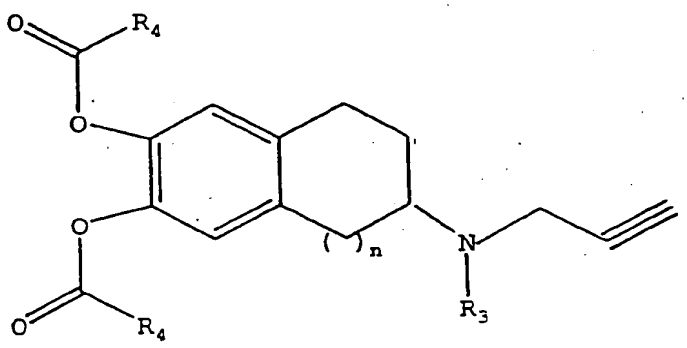


28. The compound of claim 27, wherein R_3 is Me and R_9 is Me.

29. The compound of claim 27, wherein R_3 is H and R_9 is Ph.

30. The compound of claim 27, wherein R_3 is H and R_9 is $Ph(OMe)_2$.

31. The compound of claim 1 having the structure:



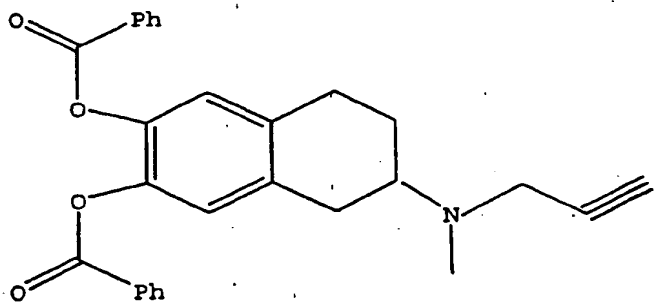
32. The compound of claim 31, wherein n is 0.

33. The compound of claim 32, wherein R_4 is Ph and R_3 is Me.

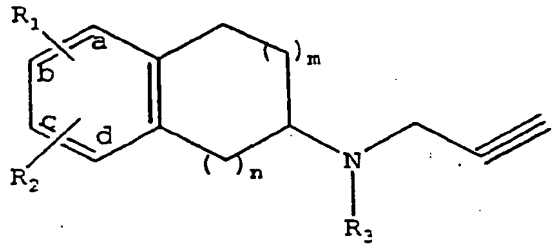
34. The compound of claim 31, wherein n is 1.

35. The compound of claim 34, wherein R_3 is Me.

36. The compound of claim 31 having the structure:



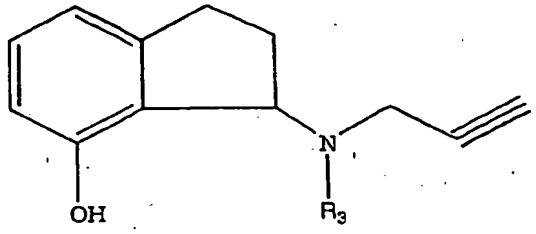
37. A compound having the structure:



wherein R_1 is OH;
wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or
R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;
wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein n is 0 or 1, and m is 1 or 2; and
wherein R_3 is H or Me when n is 1 and m is 1, or R_3 is H or C_1 to C_6 alkyl when n is 0 or m is 2,
or a pharmaceutically acceptable salt thereof.

38. The compound of claim 37, wherein the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

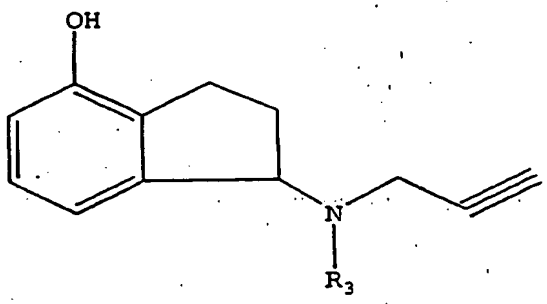
39. The compound of claim 37 having the structure:



40. The compound of claim 39, wherein R_3 is H.

41. The compound of claim 39, wherein R_3 is Me.

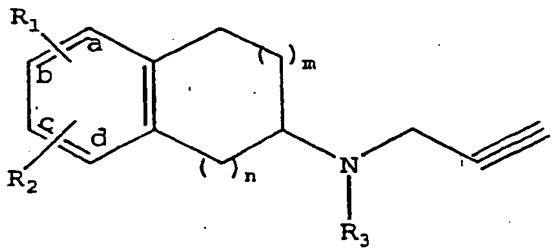
42. The compound of claim 37 having the structure:



43. The compound of claim 42, wherein R_3 is H.

44. The compound of claim 42, wherein R_3 is Me.

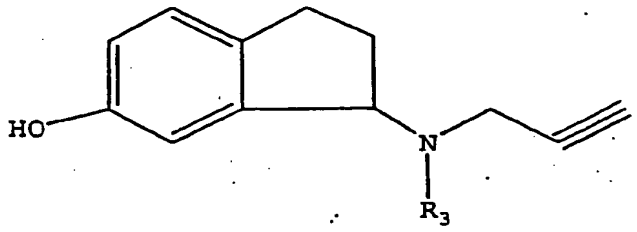
45. A compound having the structure:



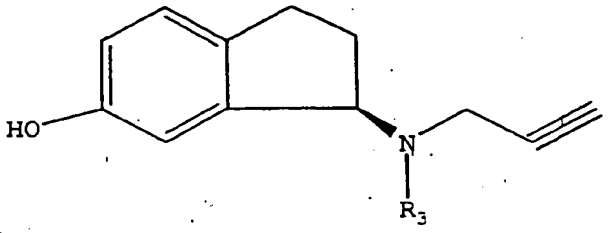
wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

46. The compound of claim 45, wherein the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

47. The compound of claim 45 having the structure:



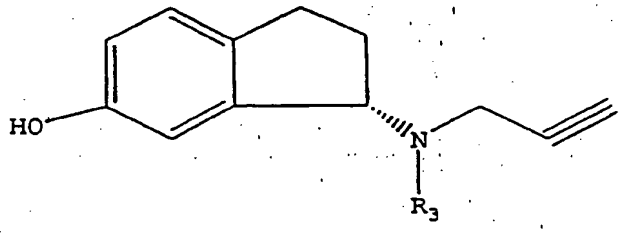
48. The compound of claim 47 having the structure:



49. The compound of claim 48, wherein R_3 is H.

50. The compound of claim 48, wherein R_3 is Me.

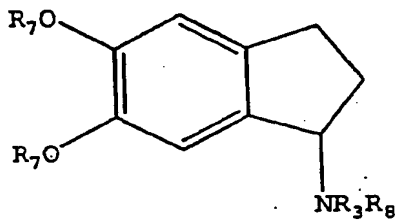
51. The compound of claim 47 having the structure:



52. The compound of claim 51, wherein R_3 is H.

53. The compound of claim 51, wherein R_3 is Me.

54. A compound having the structure:



wherein R_7 is H, C_1 to C_6 alkyl, aryl, aralkyl or $C(O)R_4$,

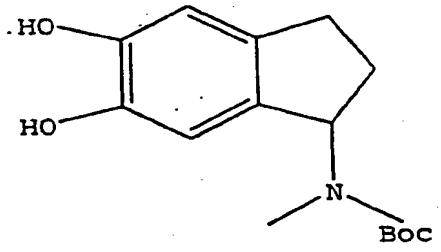
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

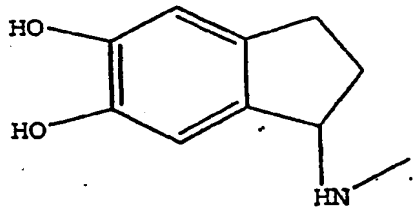
wherein R_3 is H or C_1 to C_6 alkyl;

wherein R_8 is H or t-butoxycarbonyl (Boc).

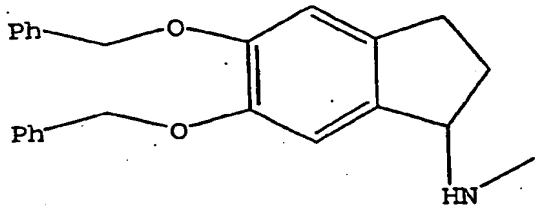
55. The compound of claim 54 having the structure:



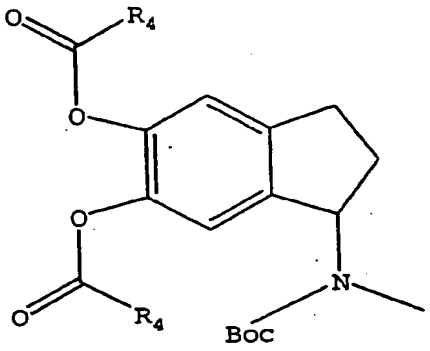
56. The compound of claim 54 having the structure:



57. The compound of claim 54 having the structure:

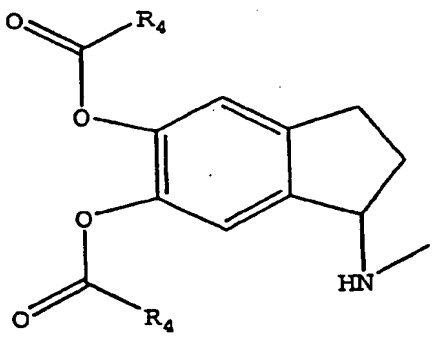


58. The compound of claim 54 having the structure:



59. The compound of claim 58, wherein R_4 is Ph.

60. The compound of claim 54 having the structure:



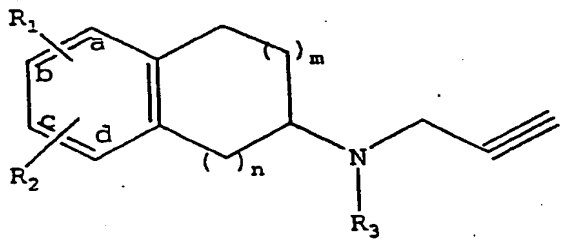
61. The compound of claim 60, wherein R_4 is Ph.

62. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound of claim 37 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

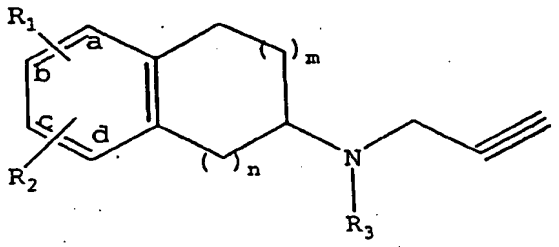
64. A pharmaceutical composition comprising the compound of claim 45 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

65. A method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;
wherein R_2 is H, OH or $OC(O)R_4$,
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

66. A method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

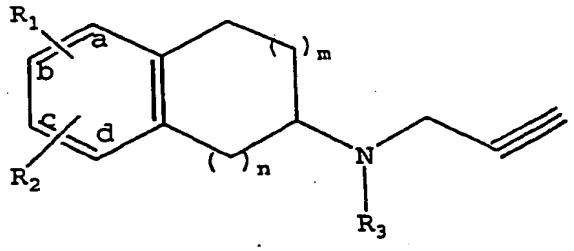
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

67. The method of claim 66, wherein the compound has the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

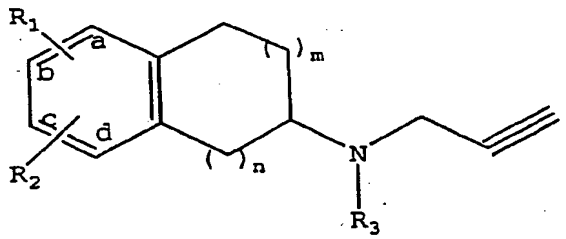
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

68. The method of claim 66, wherein the compound has the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

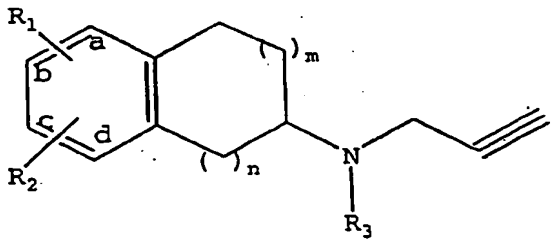
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

69. The method of claim 66, wherein the compound has the structure:



wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

70. The method of claim 66, wherein the subject is human.

71. The method of claim 66, wherein the administration comprises oral, parenteral, intravenous, transdermal, or rectal administration.

72. The method of claim 66, wherein the effective amount is from about 0.01 mg per day to about 50.0 mg per day.

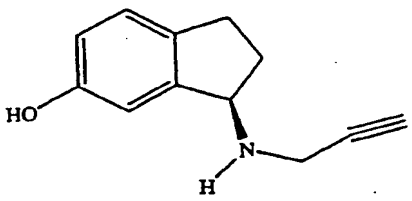
73. The method of claim 66, wherein the effective amount is from about 0.1 mg per day to about 100.0 mg per day.

74. The method of claim 73, wherein the effective amount is from about 0.1 mg per day to about 10.0 mg per day.

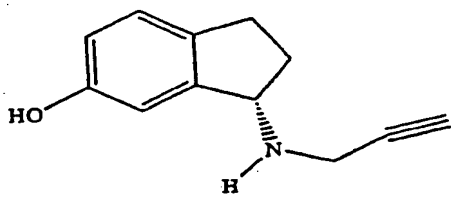
75. The method of claim 66, wherein the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome.

76. The method of claim 75, wherein the neurological disease is depression.

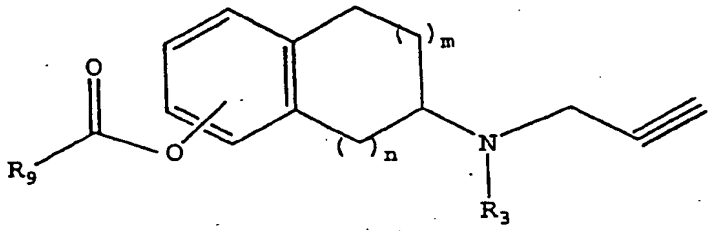
77. The method of claim 75, wherein the compound has the structure:



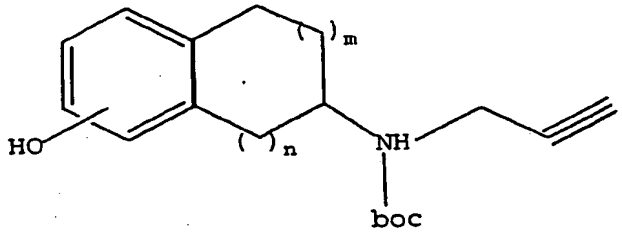
or



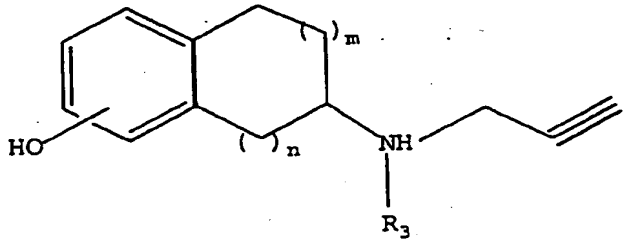
78. A process for preparing a compound having the structure:



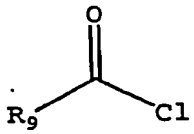
wherein n is 0 or 1, and m is 1 or 2;
wherein R_3 is H or C_1 to C_6 alkyl; and
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
comprising the step of reacting



or

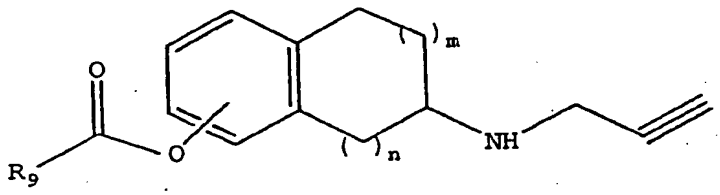


with



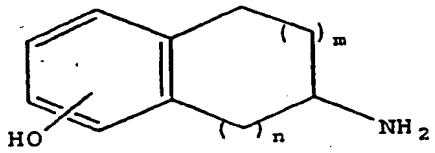
in the presence of an acid or 4-dimethylaminopyridine (DMAP) to form the compound.

79. The process of claim 78 for preparing a compound having the structure:



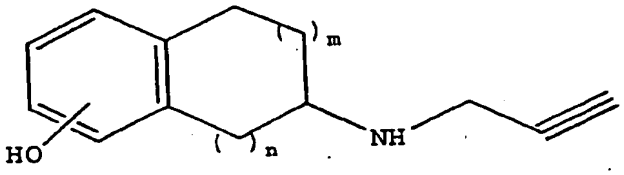
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
which process comprises:

(a) reacting a compound having the structure:

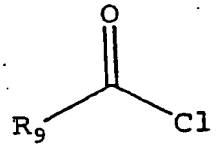


with a compound having the structure:

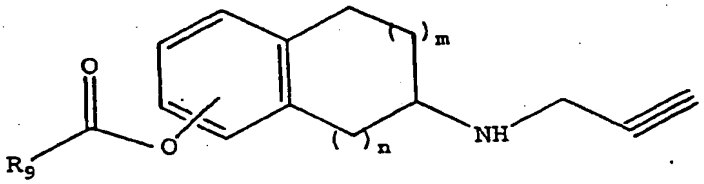
wherein X is a leaving group,
to produce a compound having the structure:



(b) reacting the compound formed in step (a) with a compound having the structure:

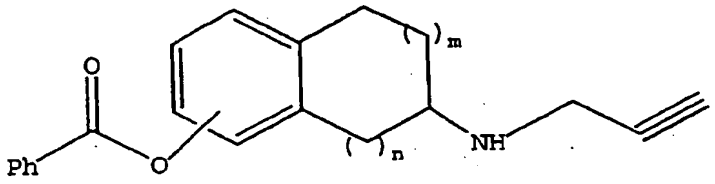


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to produce a compound having the structure:



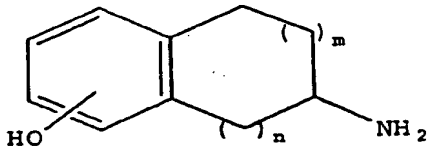
80. The process of claim 79, wherein the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (b) is $CHCl_3$.

81. The process of claim 78 for preparing a compound having the structure:

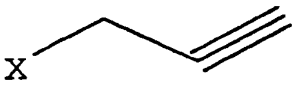


which comprises:

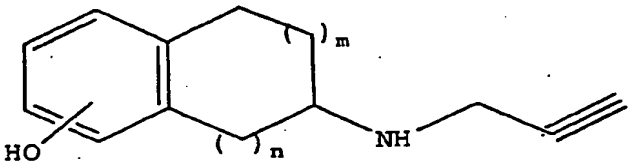
(a) reacting a compound having the structure:



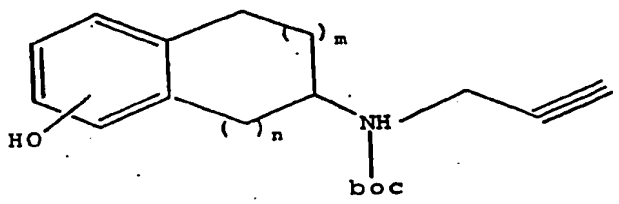
with a compound having the structure:



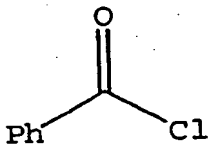
wherein X is a leaving group,
to produce a compound having the structure:



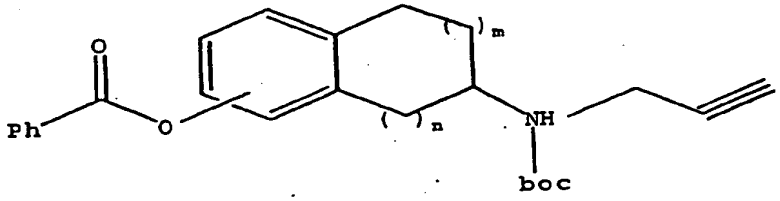
(b) N-protecting the compound formed in step (a) with tert-butoxycarbonyl (Boc) to produce a compound having the structure:



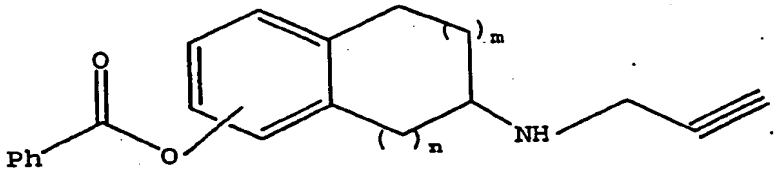
(c) reacting the compound formed in step (b) with a compound having the structure:



in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

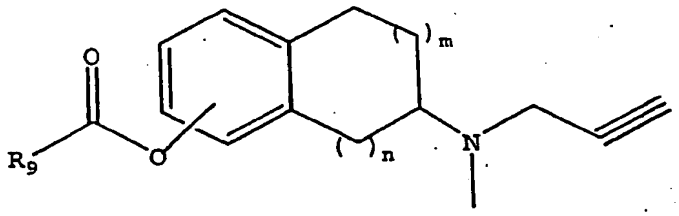


(d) deprotecting the compound formed in step (c) with HCl to produce a compound having the structure:



82. The process of claim 81, wherein the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (b) is $CHCl_3$.

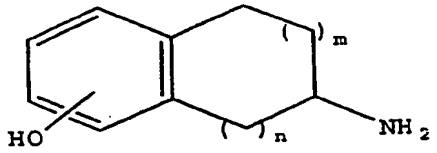
83. The process of claim 78 for preparing a compound having the structure:



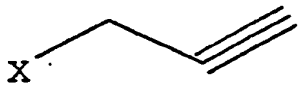
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

which process comprises:

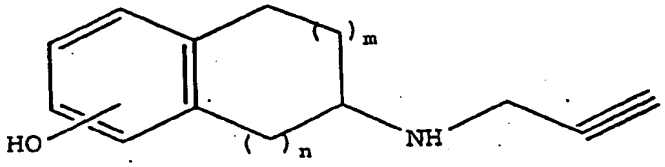
(a) reacting a compound having the structure:



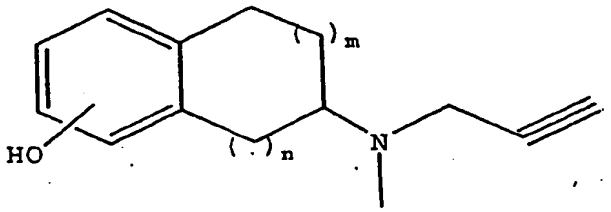
with a compound having the structure:



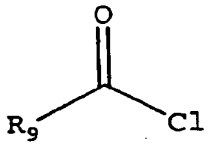
wherein X is a leaving group, to produce a compound having the structure:



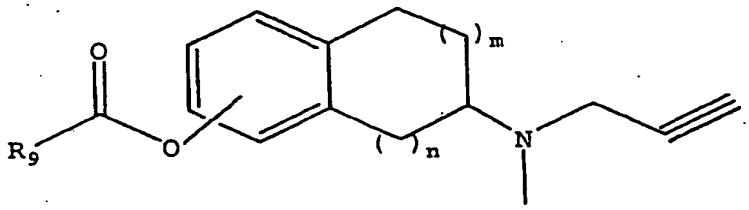
(b) reacting the compound formed in step (a) with $NaCNBH_3$ and paraformaldehyde to produce a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

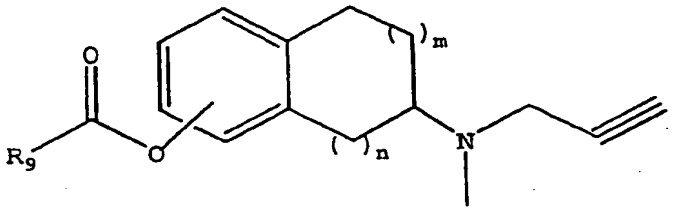


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



84. The process of claim 83, wherein the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is $CHCl_3$.

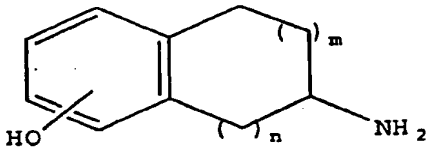
85. The process of claim 78 for preparing a compound having the structure:



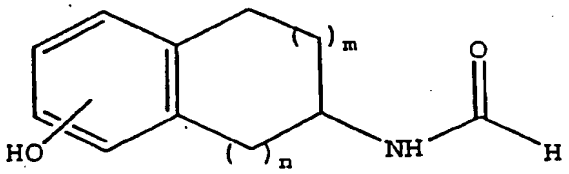
wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6;

which process comprises:

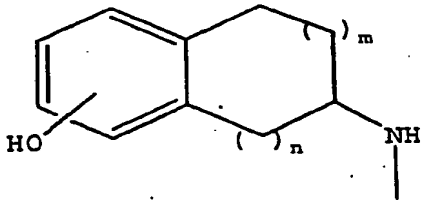
(a) reacting a compound having the structure:



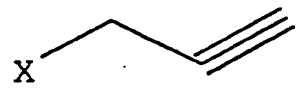
with ethyl formate to produce a compound having the structure:



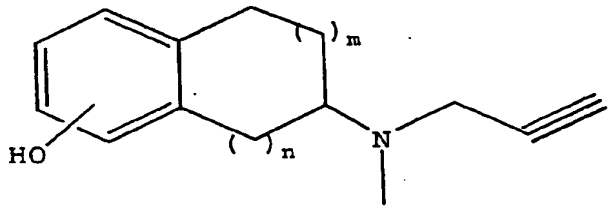
(b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:



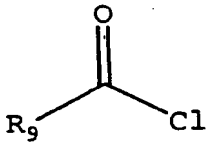
(c) reacting the compound formed in step (b) with a compound having the structure:



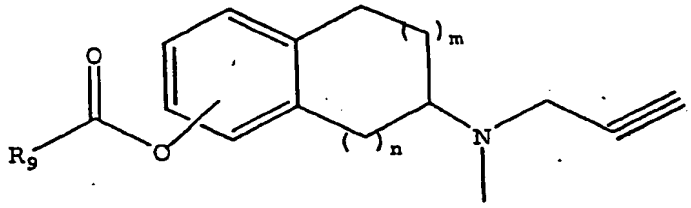
wherein X is a leaving group, to form a compound having the structure:



(d) reacting the compound formed in step (c) with a compound having the structure:

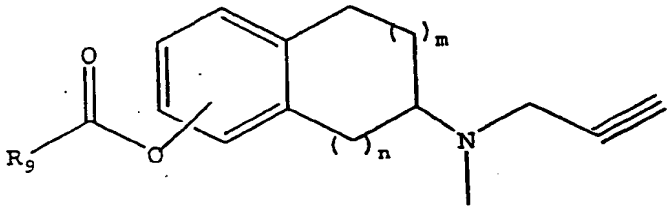


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



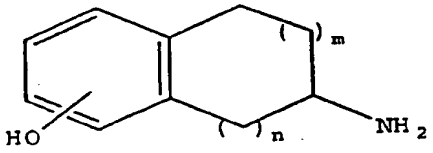
86. The process of claim 85, wherein the aprotic solvent in step (c) is $CHCl_3$.

87. The process of claim 78 for preparing a compound having the structure:

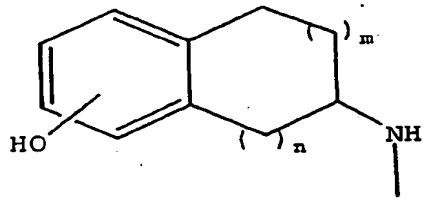


wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;
which process comprises:

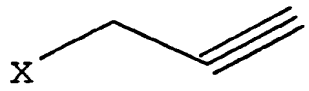
(a) reacting a compound having the structure:



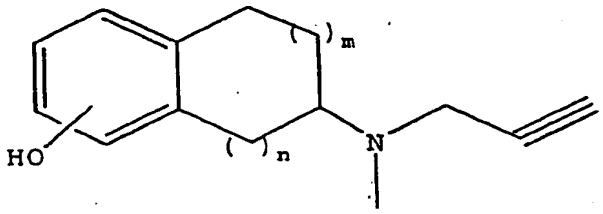
with $NaCNBH_3$/paraformaldehyde to produce a compound having the structure:



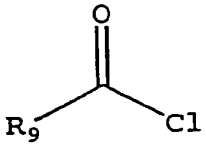
(b) reacting the compound formed in step (a) with a compound having the structure:



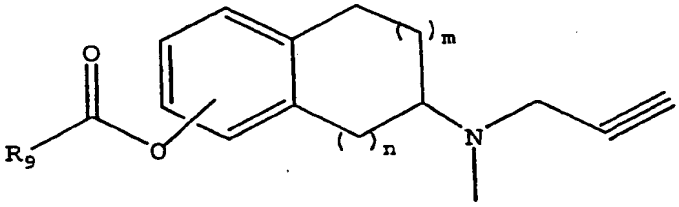
wherein X is a leaving group,
to form a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

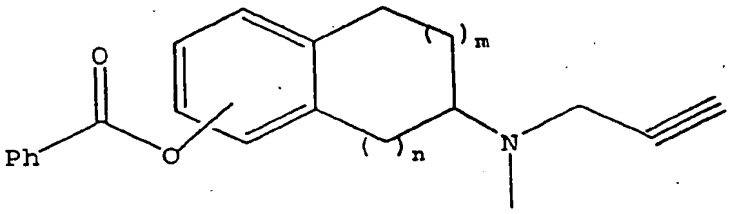


in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



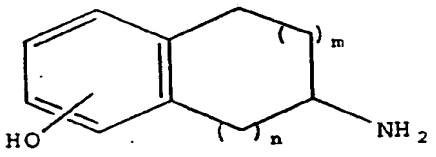
88. The process of claim 87, wherein the aprotic solvent in step (d) is $CHCl_3$.

89. The process of claim 78 for preparing a compound having the structure:



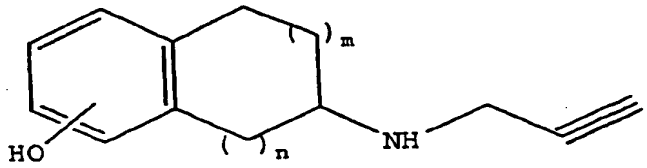
which comprises:

(a) reacting a compound having the structure:

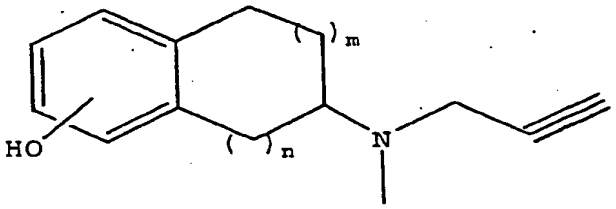


with a compound having the structure:

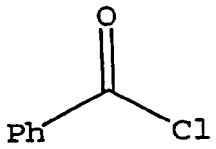
wherein X is a leaving group,
to produce a compound having the structure:



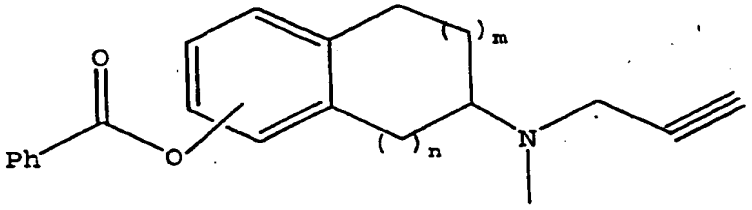
(b) reacting the compound formed in step (a) with $NaCNBH_3$ and paraformaldehyde to produce a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

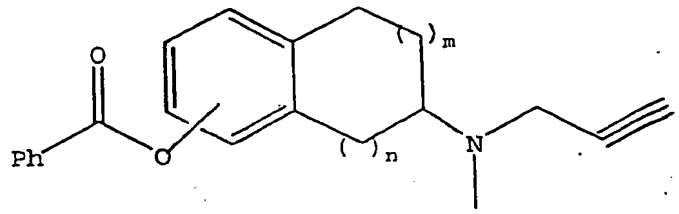


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



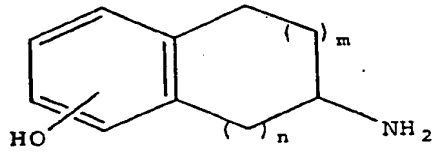
90. The method of claim 89, wherein the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is $CHCl_3$.

91. The process of claim 78 for preparing a compound having the structure:

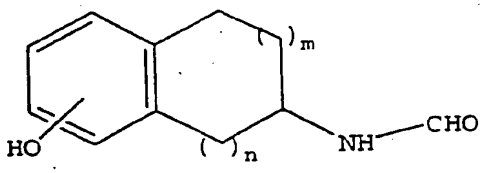


which comprises:

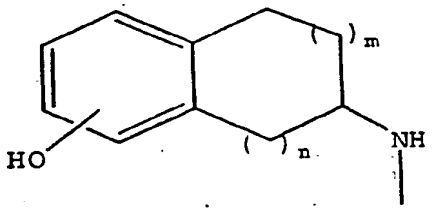
(a) reacting a compound having the structure:



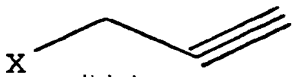
with ethyl formate to produce a compound having the structure:



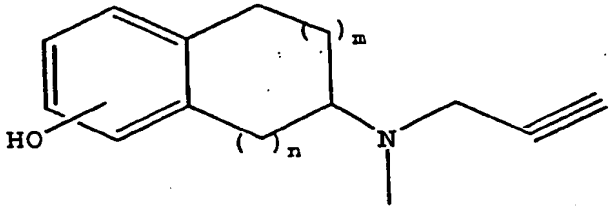
(b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:



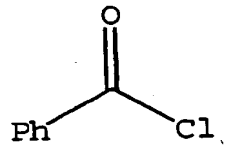
(c) reacting the compound formed in step (b) with a compound having the structure:



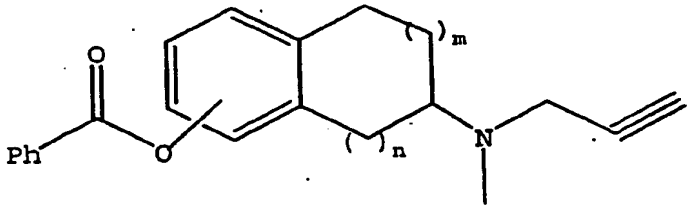
wherein X is a leaving group,
to form a compound having the structure:



(d) reacting the compound formed in step (c) with a compound having the structure:

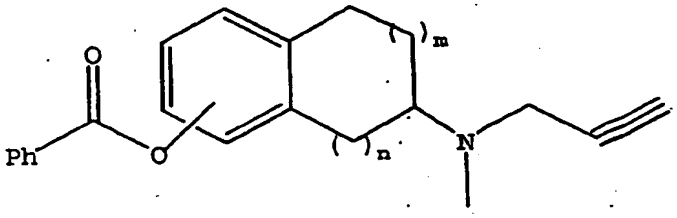


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



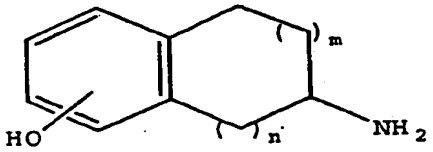
92. The process of claim 91, wherein the aprotic solvent in step (c) is $CHCl_3$.

93. The process of claim 78 for preparing a compound having the structure:

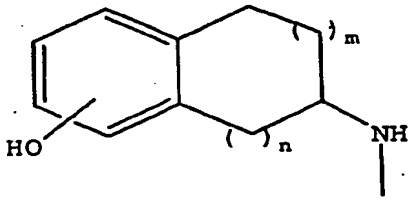


which comprises:

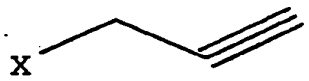
(a) reacting a compound having the structure:



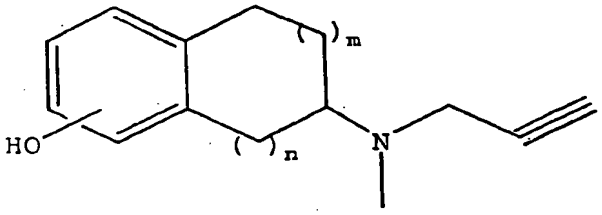
with $NaCNBH_3$/paraformaldehyde to produce a compound having the structure:



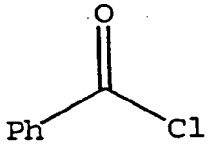
(b) reacting the compound formed in step (a) with a compound having the structure:



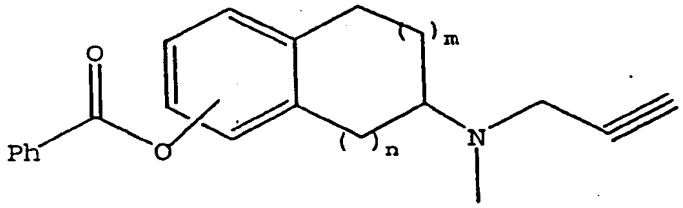
wherein X is a leaving group,
to form a compound having the structure:



(c) reacting the compound formed in step (b) with a compound having the structure:

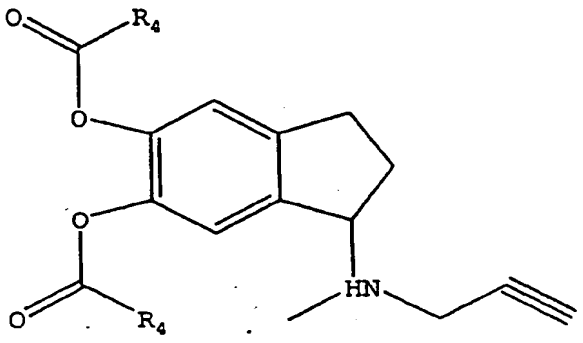


in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



94. The process of claim 93, wherein the aprotic solvent in step (d) is $CHCl_3$.

95. A process for preparing a compound having the structure:

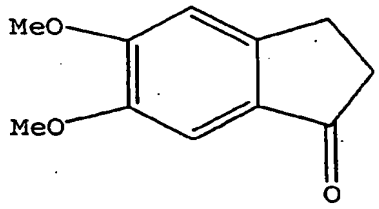


wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

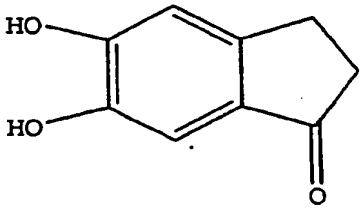
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

which process comprises:

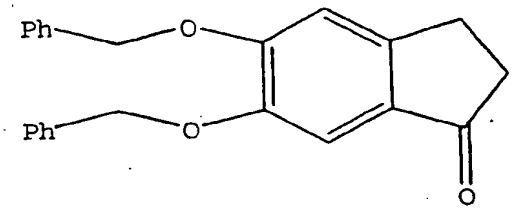
(a) reacting a compound having the structure:



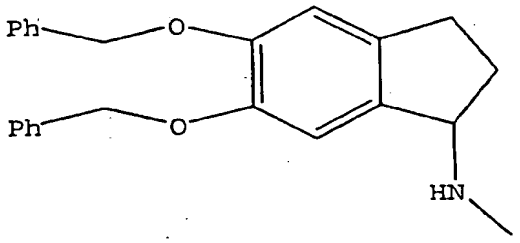
with $AlCl_3$ or BBr_3 in the presence of toluene to produce a compound having the structure:



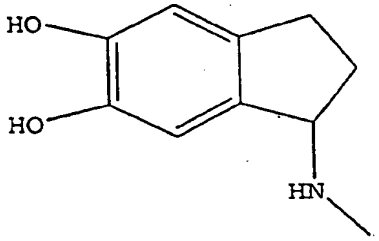
(b) reacting the product formed in step (a) with benzyl chloride and K_2CO_3 in the presence of dimethyl formamide (DMF) to produce a compound having the structure:



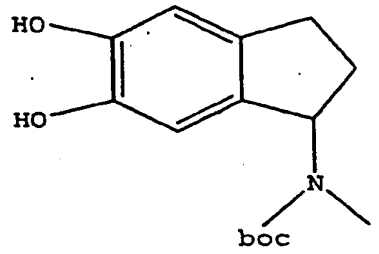
(c) reacting the product formed in step (b) with $MeNH_2 \cdot HCl$, $NaCNBH_3$ in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:



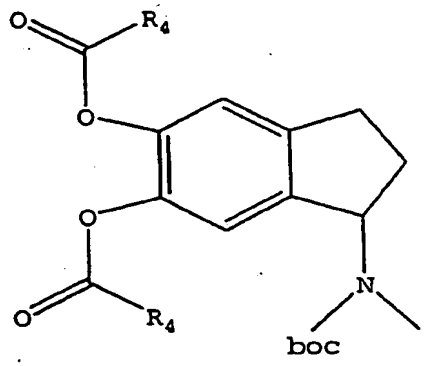
(d) reacting the product formed in step (c) with H_2, Pd/C and MeOH to produce a compound having the structure:



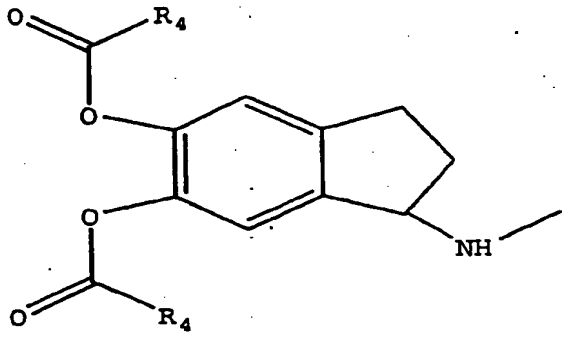
(e) reacting the product formed in step (d) with Boc_2O, dioxane/H_2O and $NaHCO_3$ to produce a compound having the structure:



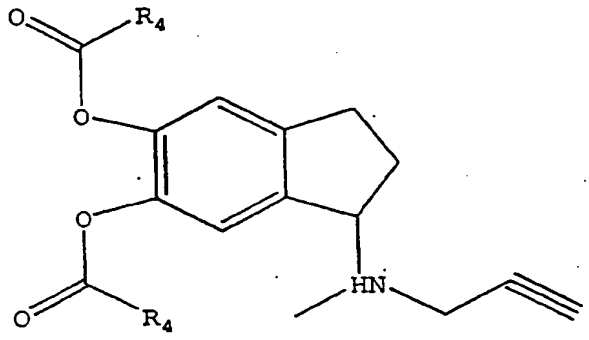
(f) reacting the product formed in step (e) with R_4COCl, Et_3N in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:



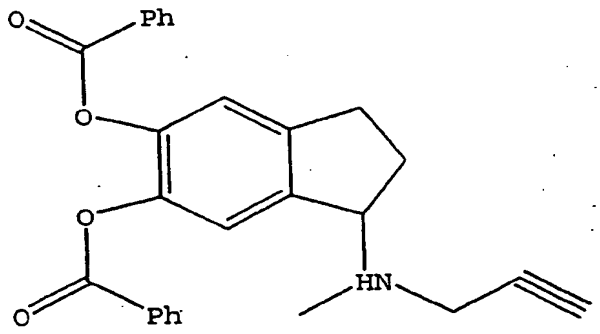
(g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:



(h) reacting the product formed in step (g) with propargyl bromide, K_2CO_3 in CH_3CN and then with HCl/ether and MeOH to produce a compound having the structure:

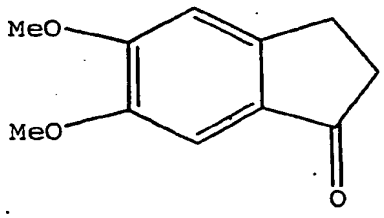


96. The process of claim 95 for preparing a compound having the structure:

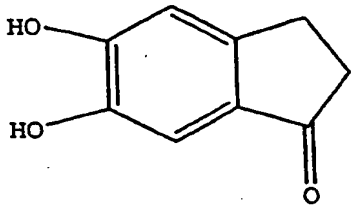


which comprises:

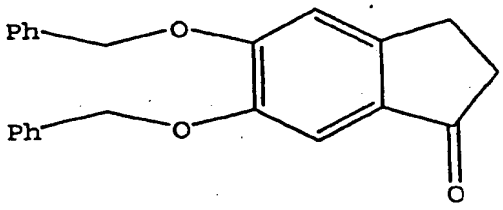
(a) reacting a compound having the structure:



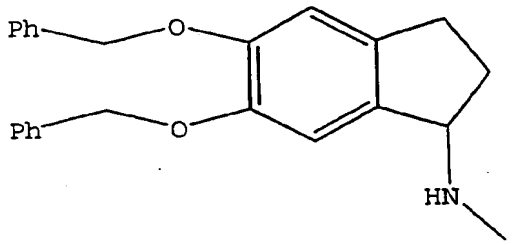
with $AlCl_3$ or BBr_3 in the presence of toluene to produce a compound having the structure:



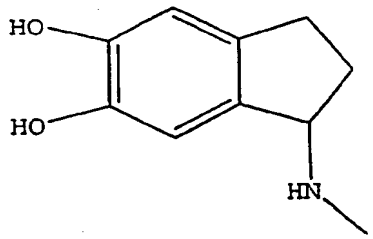
(b) reacting the product formed in step (a) with benzyl chloride and K_2CO_3 in the presence of dimethyl formamide (DMF) to produce a compound having the structure:



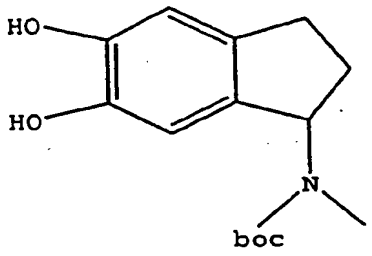
(c) reacting the product formed in step (b) with $MeNH_2 \cdot HCl$, $NaCNBH_3$ in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:



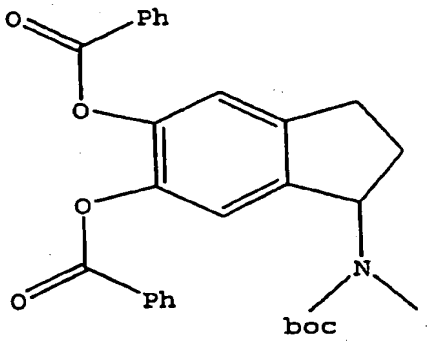
(d) reacting the product formed in step (c) with H_2, Pd/C and MeOH to produce a compound having the structure:



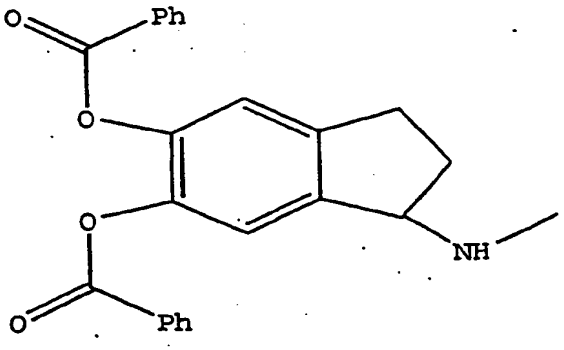
(e) reacting the product formed in step (d) with Boc_2O, dioxane/H_2O and $NaHCO_3$ to produce a compound having the structure:



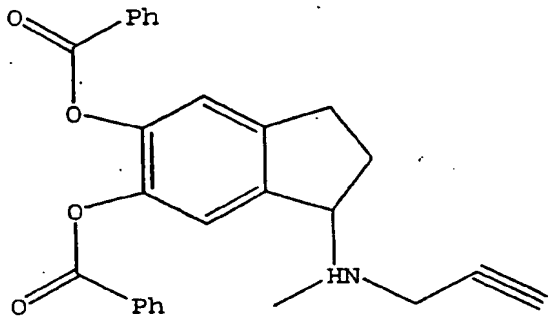
(f) reacting the product formed in step (e) with PhCOCl, Et_3N in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:



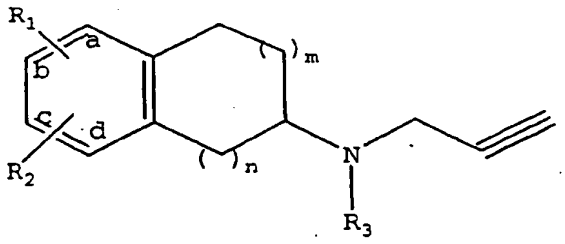
(g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:



(h) reacting the product formed in step (g) with propargyl bromide, K_2CO_3 in CH_3CN and then with HCl/ether and MeOH to produce a compound having the structure:

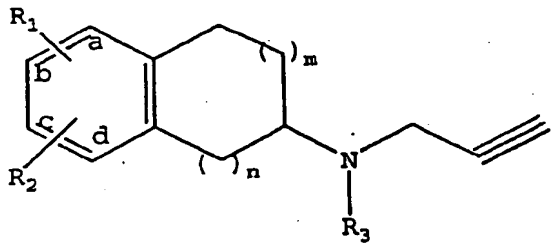


97. Use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_4$;
wherein R_2 is H, OH or $OC(O)R_4$,
wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2,
or a pharmaceutically acceptable salt thereof,
for the manufacture of a medicament for treating a subject afflicted with a neurological disease, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

98. Use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein R_1 is OH or $OC(O)R_9$, and

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl;

R_2 is H or $OC(O)R_4$, or both R_1 and R_2 are $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

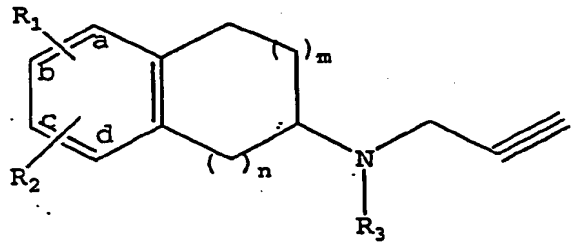
wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neurological disease in a subject, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

99. The use of claim 98, wherein the compound has the structure:



wherein R_1 is $OC(O)R_9$ and R_2 is H,

wherein R_9 is branched or unbranched C_1 to C_6 alkyl, aryl, or aralkyl, or

R_1 is $OC(O)R_4$ and R_2 is $OC(O)R_4$,

wherein R_4 is branched or unbranched C_1 to C_6 alkyl, aryl, aralkyl or NR_5R_6,

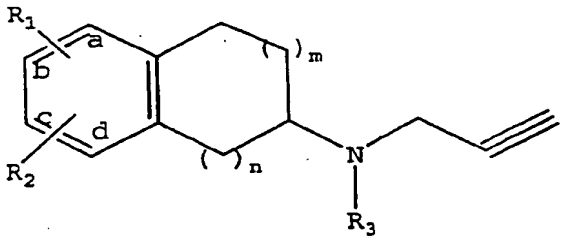
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

100. The use of claim 98, wherein the compound has the structure:



wherein R_1 is OH;

wherein R_2 is H or $OC(O)R_4$ when R_1 is attached to the "a" carbon or the "d" carbon, or

R_2 is $OC(O)R_4$ when R_1 is attached to the "b" carbon or the "c" carbon;

wherein R_4 is C_1 to C_6 branched or unbranched alkyl, aryl, aralkyl or NR_5R_6,

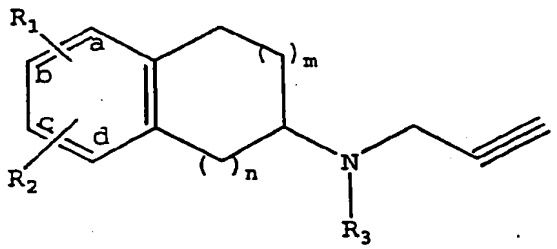
wherein R_5 and R_6 are each independently H, C_1 to C_8 alkyl, C_6 to C_{12} aryl, C_6 to C_{12} aralkyl or C_6 to C_{12} cycloalkyl, each optionally substituted;

wherein R_3 is H or C_1 to C_6 alkyl;

wherein n is 0 or 1; and

wherein m is 1 or 2.

101. The use of claim 98, wherein the compound has the structure:



wherein the compound is an optically pure enantiomer;
wherein R_1 is OH;
wherein R_2 is H;
wherein R_3 is H or C_1 to C_6 alkyl;
wherein n is 0 or 1; and
wherein m is 1 or 2.

102. The use of claim 98, wherein the subject is human.

103. The use of claim 98, wherein the medicament is formulated for orál, parenteral, intravenous, transdermal, or rectal administration.

104. The use of claim 98, wherein the therapeutically effective amount is from about 0.01 mg per day to about 50.0 mg per day.

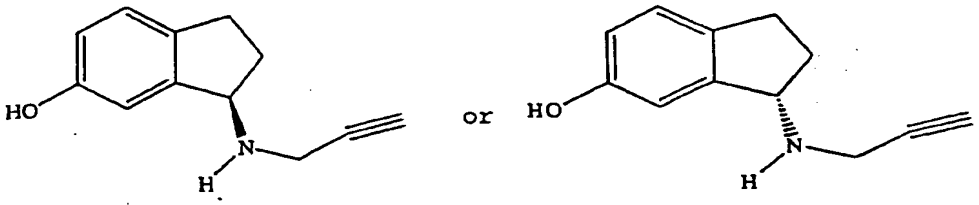
105. The use of claim 98, wherein the therapeutically effective amount is from about 0.1 mg per day to about 100.0 mg per day.

106. The use of claim 105, wherein the therapeutically effective amount is from about 0.1 mg per day to about 10.0 mg per day.

107. The use of claim 98, wherein the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis.(ALS), memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome.

108. The use of claim 107, wherein the neurological disease is depression.

109. The use of claim 108, wherein the compound has the structure:



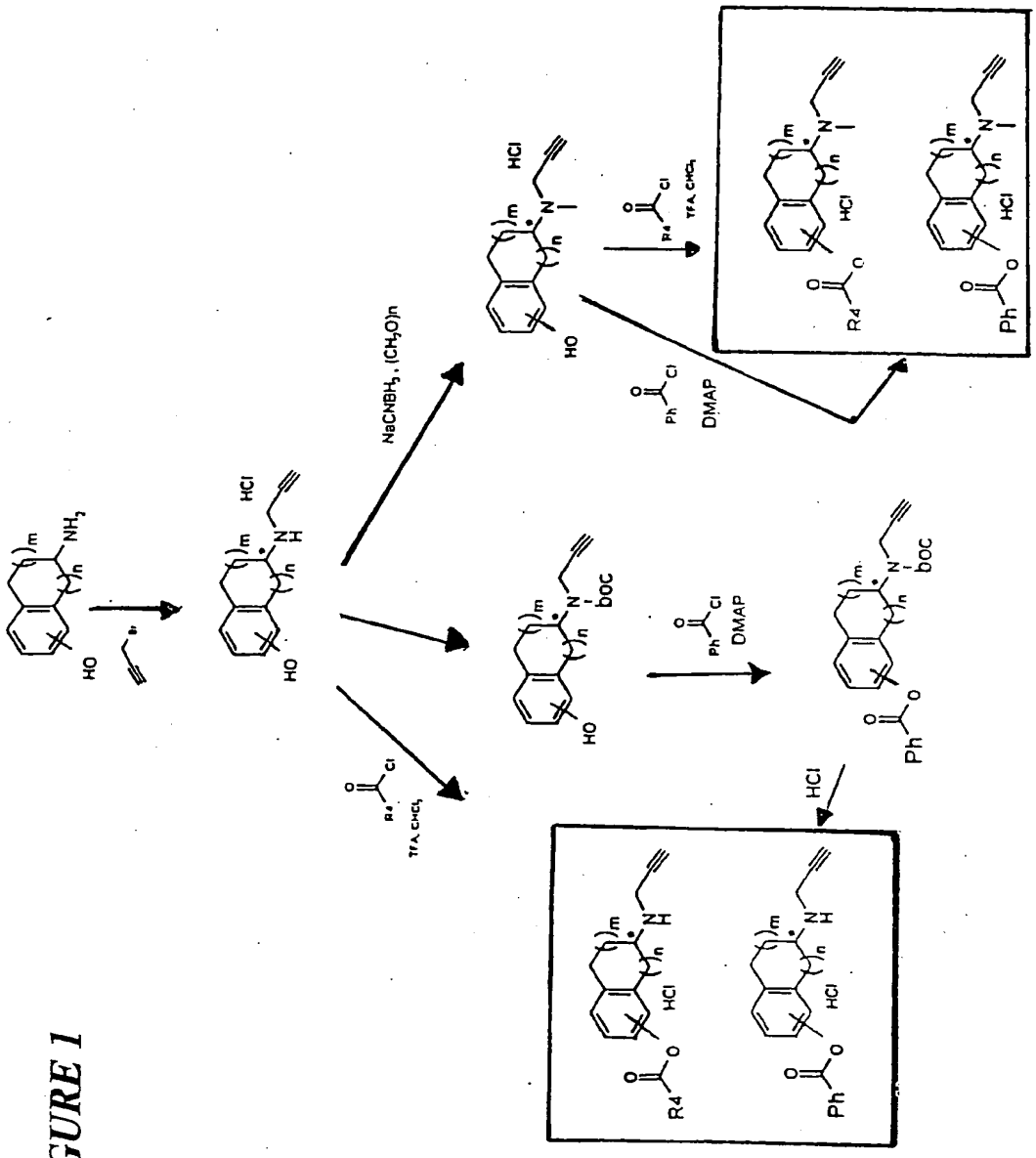
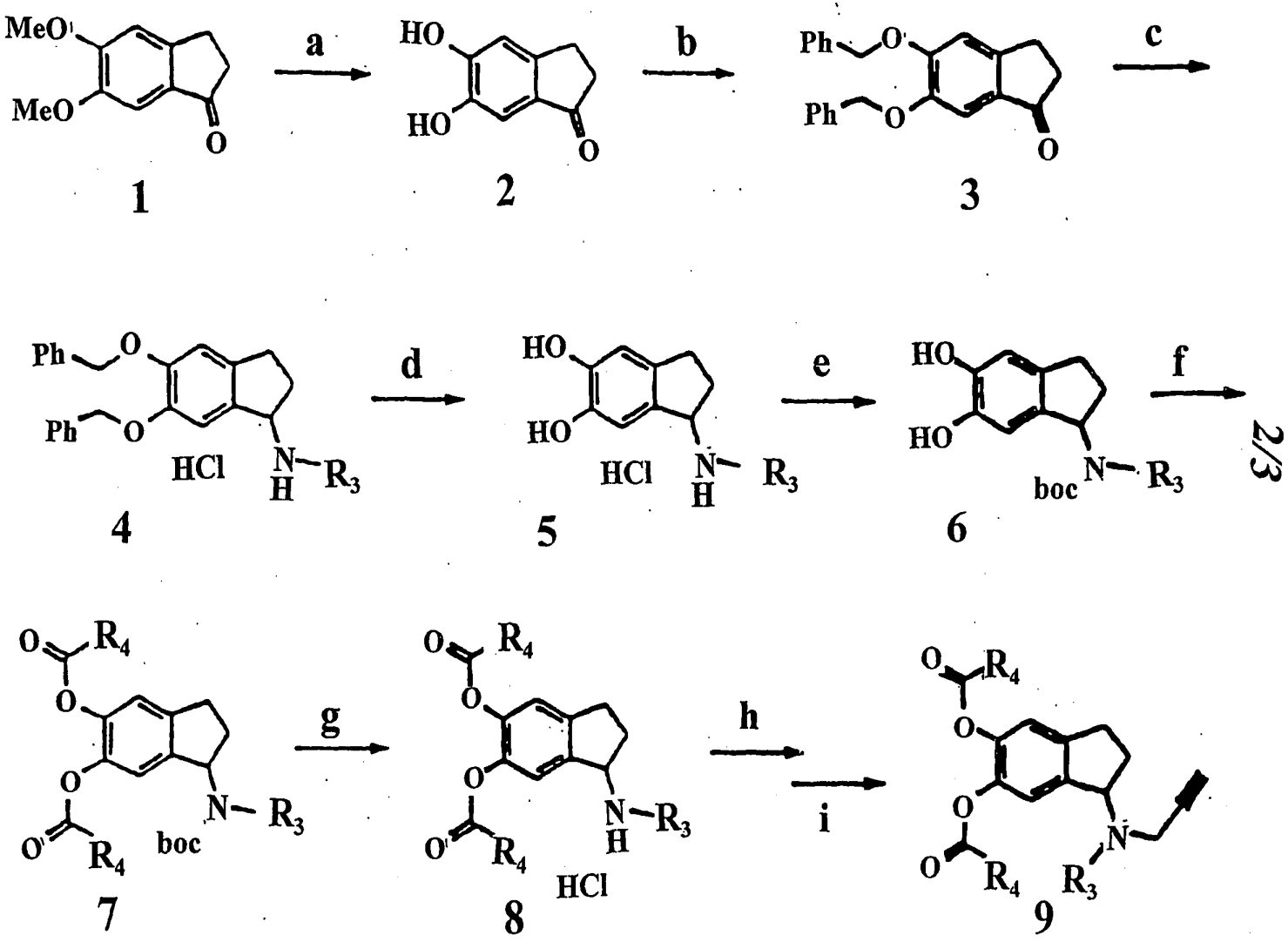


FIGURE 1

FIGURE 2


MeO
MeO
O
a
HO
HO
O
b
Ph
O
Ph
O
O
c
1
2
3
Ph
O
Ph
O
HCl
N
H
R3
d
HO
HO
HCl
N
H
R3
e
HO
HO
boc
N
R3
f
2/3
4
5
6
O
R4
O
O
O
R4
N
R3
boc
g
O
R4
O
O
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O
O
O
R4
R3
N
7
8
9

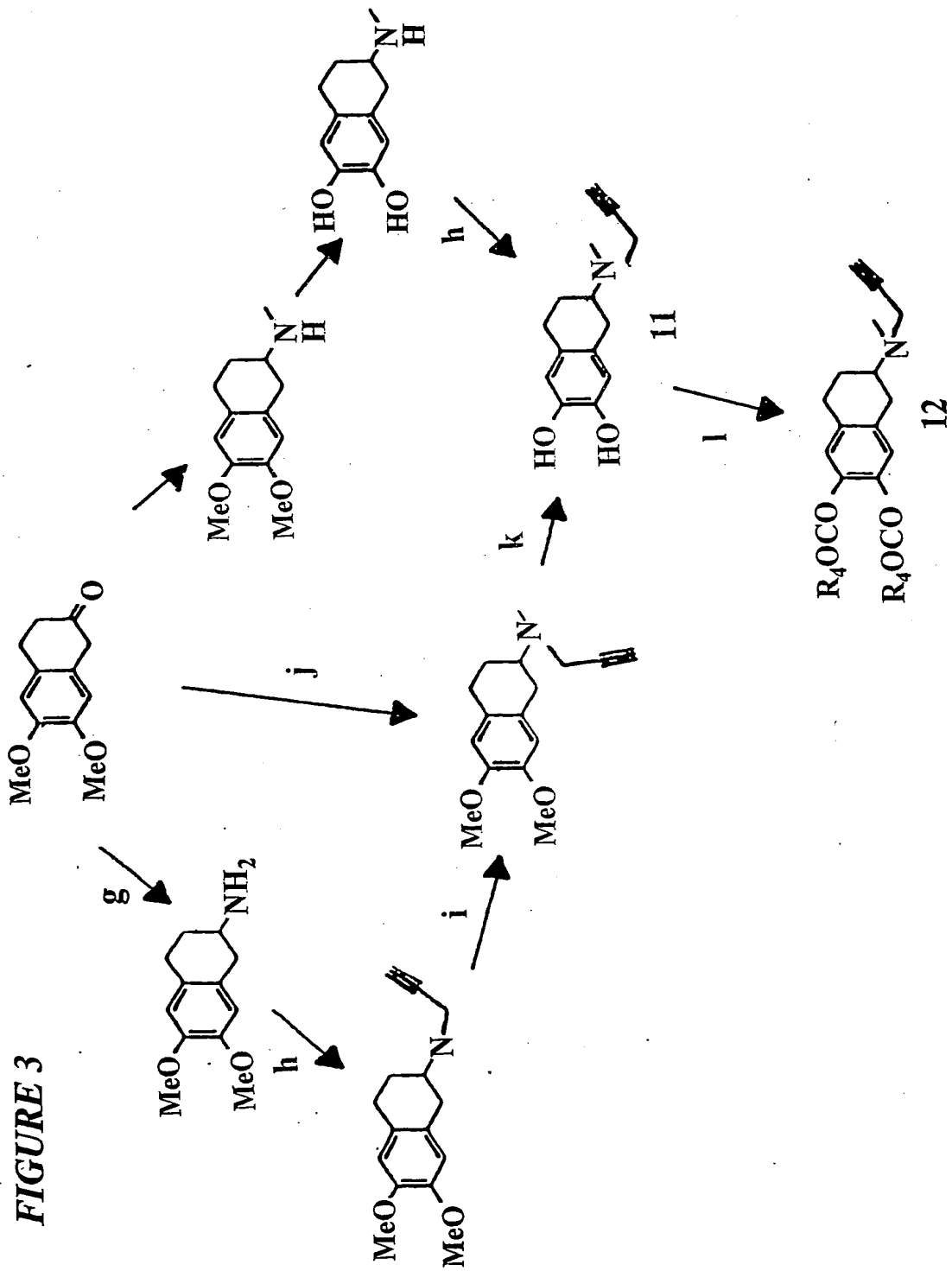

FIGURE 3